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SCIENTIFIC AMERICAN BODY

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The New Artificial Heart

Beating Limits on Transplants

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Nutraceuticals: The Truth about Nature's Cures

PLUS:

Environments for Fitness

AND: One Blood Test Tells All

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BODY
SCIENTIFIC AMERICAN

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Some of the articles in this issue are adapted and updated from articles originally appearing in Scientific American Mind, Scientific American, *and on SciAm.com.*

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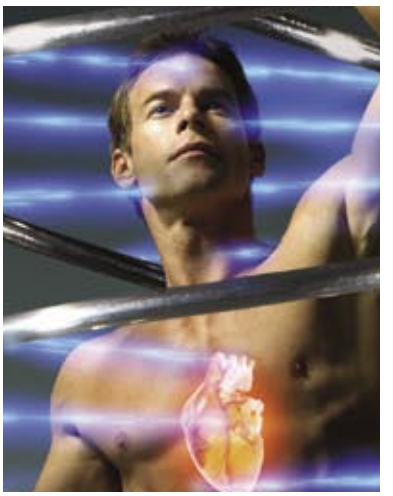

COVER IMAGE BY JAMES PORTO; MODEL MADE BY SCOTT SIKEN

The Science of Staying Well

Throw the word "health" at Google, and you will retrieve, as I write this, about 958 million results. Alternatively, if you feel up to reading them, you could directly consult the medical journals for information; the National Library of Medicine's MEDLINE service indexes about 5,000 of them. If you are into health and fitness magazines, you probably have more than 100 of those to choose from.

Clearly, a world of health information is out there and readily available if you want it. The problem is one of navigating through it to worthy destinations. Finding your way to relevant, trustworthy information, presented in terms that are not only understandable but appealing to your interests, is still a challenge.

That is why we dare to think the magazine you hold in your hands, *Scientific American Body,* has something special to offer to the curious health consumer. *Scientific American* has been covering new developments in medicine, science and technology for more than 162 years. It brings together leading health professionals and experienced journalists to explain the significance of new discoveries, the state of current knowledge and the bright possibilities just coming over the horizon. And as the realm of knowledge about health and medicine continues to expand, *Scientific American* is proud to present new offerings in print and online to keep you informed about it.

We believe that sophisticated health readers want more than a service-oriented breakdown of what to eat, what drugs to take and how to exercise. *Scientific American Body* therefore brings you just enough of the science underlying health recommendations for you to draw your own conclusions about their solidity or even their safety. Yet we also realize that health and wellness is not purely a matter of medical science—that there is an artistry to healing that needs to take into account the whole of a person. Thus, *Body* also includes voices of personal testimonial, discussing their own experiences with illness, recovery and prevention. We are also eager to take a clear-eyed look at the state of alternative medicine and to hail it for its successes or to criticize it for its failures, depending on what the data show.

But *Body* is more than just this printed issue. Follow its links online to www.SciAm.com/Body, where you can further explore all these health topics and many more, through the full informational resources of *Scientific American.* You will also find there growing communities of patients, family members and health professionals ready to share their insights and hear what you have to say, too.

Read on and be well.

John Rennie
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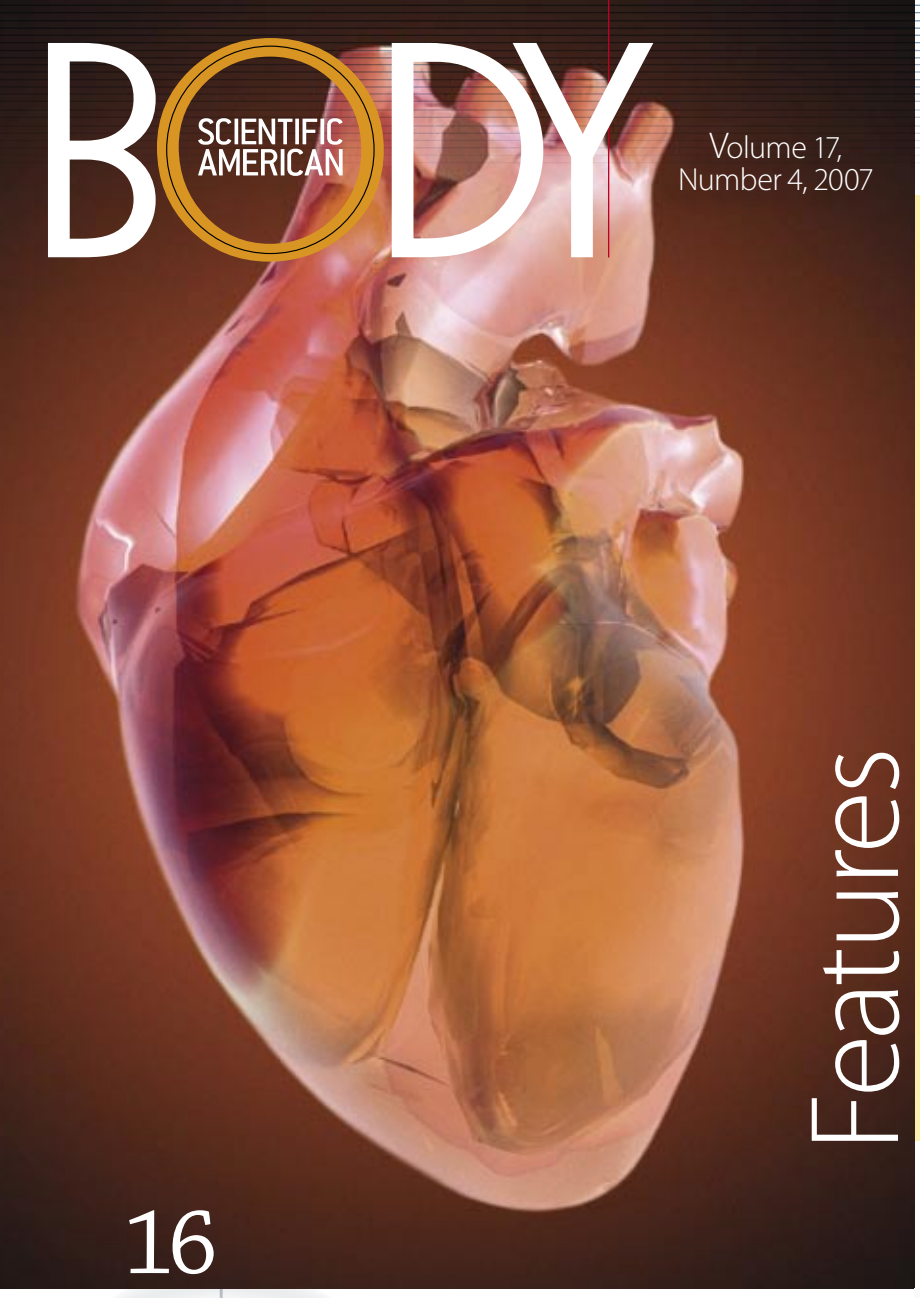
SCIENTIFIC AMERICAN BODY

Volume 17, Number 4, 2007



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MEHAU KULYK *SPL/Photo Researchers, Inc. (heart)*

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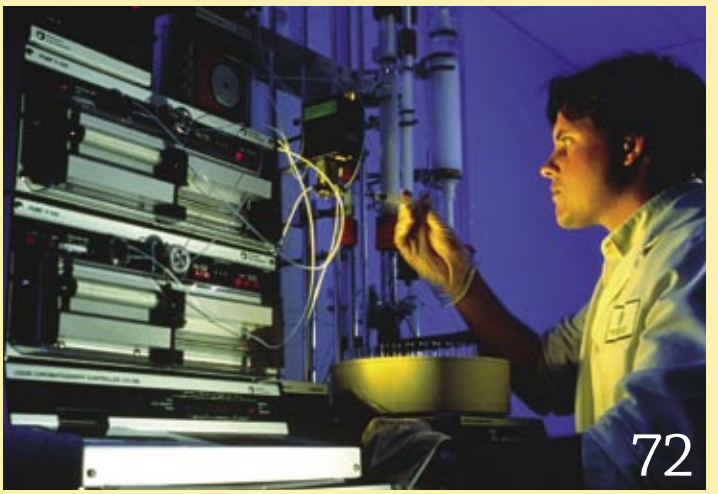

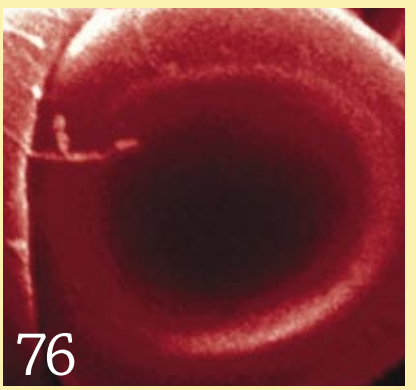

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Scientific American Special (ISSN 1936-1513), Volume 17, Number 4, 2007, published by Scientific American, Inc., 415 Madison Avenue, New York, NY 10017-1111.

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Canadian BN No. 127387652RT; QST No. Q1015332537. To purchase additional quantities: U.S., $10.95 each; elsewhere, $13.95 each. Send payment to Scientific American, Dept. BD2007, 415 Madison Avenue, New York, NY 10017-1111. **Inquiries: fax 212-355-0408 or telephone 212-451-8442.** Printed in U.S.A.

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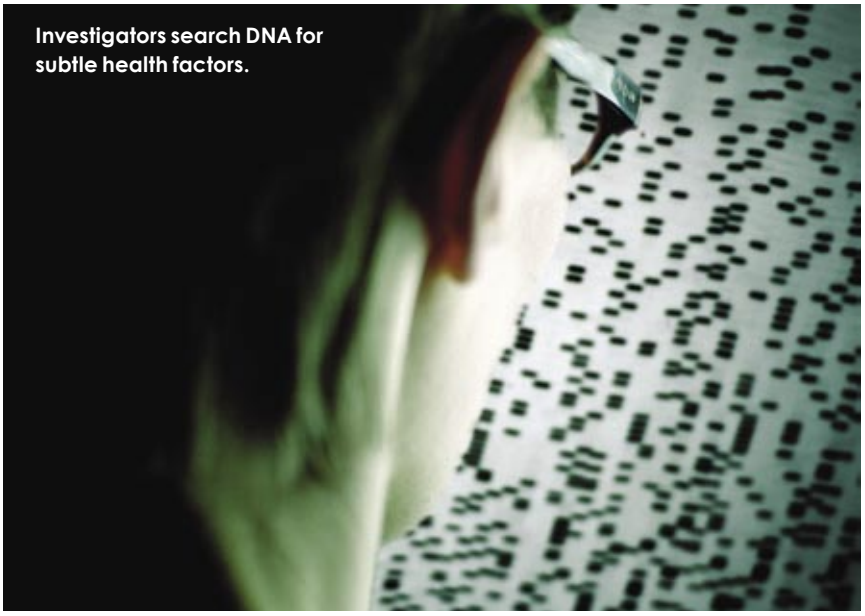
Genomics

Weighing Risks Written in DNA

IS THE PUBLIC READY TO KNOW PERSONAL GENETIC INFORMATION?

By Christine Soares

A CHANCE TO PEEK INTO THE FUTURE—at least one possible future—is always a tempting fantasy. But would you take it? And if you didn't like what you saw, how hard would you try to change it? After almost 20 years spent reading, mapping and analyzing human DNA, researchers at the National Human Genome Research Institute (NHGRI) believe that personal genetic information is nearly ready for use by consumers in managing their health. To determine whether that is so, however, the institute is launching a large-scale study.



Investigators search DNA for subtle health factors.

ROBERT DALY *Getty Images*

The year-long Multiplex Initiative will ultimately involve thousands of subjects, who will be offered a personal genetic report card based on screening for gene variations associated with increased risk for major diseases. The investigators are interested in how many take up the offer and why and how participants respond to their results. The researchers also hope to gain insights into the best ways for health professionals to communicate information about genetic risk.

"Our major outcomes and measures are going to be [whether] they understand the tests, because this is hard stuff to package for the general public," explained senior investigator Lawrence Brody of the NHGRI's Genome Technology branch, when announcing the initiative in early May in Washington, D.C. "And whether or not they find the test useful, what are their attitudes about it."

The investigators are recruiting among members of the Henry Ford Health System, a Detroit-area HMO, and will follow up with participants to see if learning genetic information about themselves prompts them to seek out wellness programs or change any behaviors. As many as 10,000 potential participants between the ages of 25 and 40 will have received mailed invitations to be screened for versions of some 15 genes associated with higher risk for conditions such as coronary artery disease, osteoporosis, lung cancer, colorectal cancer and melanoma.

"I think the NHGRI study is very valuable," says Catherine Schaefer, the lead investigator of a larger Kaiser Permanente research project that is currently recruiting among 3.5 million members of that California HMO. Schaefer is gathering DNA samples and other health information in the hope of discovering new gene variants that confer disease risk or protection. "It's important to learn how people respond to this very complex genetic information," she says.

In the past, genetic testing has been mostly limited to single-gene diseases, such as Huntington's or cystic fibrosis, where the grim association between particular genes and eventual illness is clear and certain. Complex conditions, in contrast, might involve the activity of hundreds or thousands of genes in different aspects or stages of the disease, and diet or other environmental factors may also interact with those genes over a lifetime.

"For better or worse, we've convinced the public that genetics is very important and deterministic," Brody explained. "And now we have to back off of that a little bit."

All the conditions included in the Multiplex Initiative screening are preventable, so participants can decide for themselves whether the results are worth acting on. Current measures of future risk typically rely on symptoms that have already appeared, such as high blood pressure or spinal degeneration, noted NHGRI director Francis Collins during the announcement. Genetic testing, he said, gives people an opportunity "so that you can begin to practice prevention before you're already half in the grave."

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Medicine/Children

Nipping Childhood Obesity in the Bud

MOTHERS' GESTATIONAL DIABETES MIGHT LATER TEND TO MAKE THEIR KIDS FATTER

By Lisa Stein

Add yet another reason for women to make sure they eat right and get plenty of exercise: if they don't, their children may be at greater risk for becoming obese.

Three to 8 percent of pregnant women in the U.S. each year develop gestational diabetes, a transient blood glucose condition that ends after delivery. As has long been known, those women are at higher risk for related health problems and for having abnormally large infants whose births may require either C-sections or potentially dangerous natural deliveries.

Endocrinologist Teresa Hillier and her colleagues at the Kaiser Permanente Center for Health Research (CHR) in Portland, Ore., and Honolulu analyzed the medical records of 9,439 women who gave birth between 1995 and 2000. They discovered that tots of pregnant women with untreated high blood glucose levels were 89 percent more likely to be overweight and 82 percent more likely to be obese by the age of five to seven years. (Plumping up during that period of childhood is considered one predictor of adult obesity.) "This suggests that you're metabolically programming your child to become obese because of being overfed in the womb," Hillier says.

The good news in the CHR team's findings, however, is that controlling pregnant moms' gestational diabetes (with diet and exercise or with insulin injections) could significantly reduce the chances of their tykes becoming tubby. In fact, Hillier notes, the children of stricken women who were successfully treated had the same risk of becoming obese as the kids of women with normal blood glucose levels throughout pregnancy.

Hillier's advice to expecting mothers: make sure that your ob-gyn screens for high blood sugar levels (generally between the 24th and 28th weeks of pregnancy) and, if you are diagnosed with the condition, that you are treated and stick with the program. "It's the best thing you can do," she says, "to reduce your child's risk of obesity."

The study, the largest of its kind, was funded by the American Diabetes Association (ADA) and appears in the September issue of the ADA's journal, *Diabetes Care*.

STEVEN WHITE *Getty Images (top)*; TIM PLATT *Getty Images (bottom)*

Nutrition

Hyperactive kid? Maybe it's the food coloring.

Children who consumed a sweetened drink laden with common food-coloring agents and the preservative sodium benzoate were more hyperactive than those who drank identical beverages minus the additives, according to a study published this past September in the *Lancet*. Parents and teachers rated kids' activity levels after downing the refreshments, finding that those who consumed the coloring and preservative were 10 percent more hyper. The researchers say the survey bolsters the debated notion that additives give kids an extra kick. *—JR Minkel*

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Environment

World's Top 10 Most Polluted Places

WHERE TOXIC POLLUTION AND HUMAN HABITATION COLLIDE WITH DEVASTATING EFFECTS **By David Biello**

1 **SUMQAYIT, AZERBAIJAN**—This area gained the dubious distinction of landing atop the Blacksmith Institute's list of the world's most polluted sites. Yet another heir to the toxic legacy of Soviet industry, this city of 275,000 bears heavy metal, oil and chemical contamination from its days as a center of chemical production. As a result, locals suffer cancer rates 22 to 51 percent higher than their countrymen, and their children suffer from a host of genetic defects, ranging from mental retardation to bone disease.

"As much as 120,000 tons of harmful emissions were released on an annual basis, including mercury," says Richard Fuller, founder of Blacksmith, an environmental health organization based in New York City. "There are huge untreated dumps of industrial sludge."

2 **CHERNOBYL, UKRAINE**—The fallout from the world's worst nuclear power accident continues to accumulate, affecting as many as 5.5 million people and leading to a sharp rise in thyroid cancer. The incident has also blighted the economic prospects of surrounding areas and nations.

3 **DZERZHINSK, RUSSIA**—The 300,000 residents of this center of cold war chemical manufacturing have one of the lowest life expectancies in the world thanks to waste injected directly into the ground. "Average life expectancy is roughly 45 years," says Stephan Robinson, a director at Green Cross Switzerland, an environmental group that collaborated on the report. "Fifteen to 20 years less than the Russian average and about half a Westerner's."

4 **KABWE, ZAMBIA**—The second largest city in this southern African country was home to one of the world's largest lead smelters until 1994. As a result of that industry, the entire city is contaminated with the heavy metal, which can cause brain and nerve damage in children and fetuses.

5 **LA OROYA, PERU**—Although this is one of the smallest communities on the list (population 35,000), it is also one of the most heavily polluted because of extensive lead, copper and zinc mining by the U.S.–based Doe Run mining company.

6 **LINFEN, CHINA**—A city in the heart of China's coal region in Shanxi Province, Linfen is home to three million inhabitants, who choke on dust and air pollution and drink arsenic that leaches from the fossil fuel.

7 **NORILSK, RUSSIA**—This city above the Arctic Circle contains the world's largest metal-smelting complex and some of the planet's worst smog. "There is no living piece of grass or shrub within 30 kilometers of the city," Fuller says. "Contamination [with heavy metals] has been found as much as 60 kilometers away."

Geiger counter measures radiation near the Chernobyl reactor site.

JOSEPH SYWENKYJ *Redux*

8 **SUKINDA, INDIA**—Home to one of the world's biggest chromite mines—chromite makes steel stainless, among other uses—and 2.6 million people. The waters of this valley contain carcinogenic hexavalent chromium compounds courtesy of 30 million tons of waste rock lining the Brahmani River.

9 **TIANYING, CHINA**—The center of Chinese lead production, this town of 160,000 has lead concentrations in its air and soil that are 8.5 to 10 times those of the national health standards. The concentrations of lead dusting the local crops are 24 times too high.

10 **VAPI, INDIA**—This town at the end of India's industrial belt in the state of Gujarat houses the dumped remnant waste of more than 1,000 manufacturers, including petrochemicals, pesticides, pharmaceuticals and other chemicals. "The companies treat wastewater and get most of the muck out," says David Hanrahan, Blacksmith's London-based director of global operations. "But there's nowhere to put the muck, so it ends up getting dumped."

The Blacksmith Institute compiled the above list, which extends to 20 more sites in its "Dirty 30," by comparing the toxicity of the contamination, the likelihood of it getting into humans and the number of people affected. Places were bumped up in rank if children were impacted. No U.S. or European sites made the list thanks to a mop-up of lingering human health hazards over the past several decades, but that trend does not absolve the developed world of all responsibility. "The nickel we use in our cars or elsewhere is likely to have come from Norilsk," Fuller notes. "And some of the lead in our car batteries will have come from one of these places."

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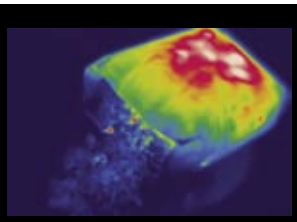

Popcorn's dark side

A 53-year-old Colorado man who ate two bags of microwaved popcorn daily for 10 years apparently developed bronchiolitis obliterans—"popcorn worker's lung," a debilitating disease previously seen only among workers at popcorn factories. Medical researchers suspect that inhaled diacetyl, the chemical that gives microwave popcorn its sinful buttery flavor, gradually inflames and scars the lungs' tiny air sacs, making it increasingly difficult for sufferers to exhale.

Cecile Rose, a physician who specializes in the disorder at the National Jewish Medical and Research Center in Denver, alerted the U.S. Food and Drug Administration in July that her coughing patient's Colorado home had diacetyl levels similar to those in factories. But the news only became public in September on a health policy blog that accused regulators of ignoring the potential risk to popcorn lovers. Four major popcorn manufacturers quickly announced they would phase out diacetyl. ***—JR Minkel***

SCIENTIFICA/GETTY IMAGES (*left*); DAVID ALAN HARVEY (*right*)

Mental Health

Suffering a Slow Recovery

FAILED REBUILDING AFTER KATRINA SETS OFF A MENTAL HEALTH CRISIS

By Emily Harrison

Residents of the 7th Ward of New Orleans still suffer after Hurricane Katrina.

There may be a new roof on the New Orleans Superdome and tourists in the French Quarter, but time is not healing all wounds in the wake of Hurricane Katrina. Even two years after the storm, mental health problems in the region are growing among the nearly 70,000 families still living in temporary housing provided by the Federal Emergency Management Agency (FEMA). The slow recovery, researchers and clinicians are finding, has bred levels of mental distress unseen in the aftermath of other disasters.

"Most of the time, distress emerges early and dissipates over the first year post-disaster," says psychologist Fran Norris of the National Center for Posttraumatic Stress Disorder at Dartmouth Medical School. Not so with Hurricane Katrina. One year after the storm a Harvard Medical School committee funded by the National Institute of Mental Health reported doubled rates of depression and anxiety in the region.

A team led by David Abramson of the National Center for Disaster Preparedness (NCDP) at Columbia University, in collaboration with the Children's Health Fund, surveyed residents of FEMA-provided trailers and hotels in Louisiana and reported widespread clinically diagnosed psychiatric problems. Sixty-eight percent of female caregivers and 44 percent of children suffered new mental health issues, including depression, anxiety and sleep disorders. When the Columbia team surveyed a similar group in Mississippi six months later, it found even higher rates of distress despite the fact that Mississippi had suffered less damage and had an additional half a year to recover.

"A disaster is an abnormal event, and people being affected by that is normal," allows Anthony Speier of the Office of Mental Health at the Louisiana Department of Health and Hospitals. "But Katrina falls into the realm of a catastrophic event. We are not set up to help a population recover from that," he adds.

Katrina differs from other storms not only for the sheer magnitude of havoc it left but also for the stymied rebuilding efforts following it. Most neighborhoods have remained deserted, with negligible visible change in the past year, according to Speier. This open-ended holding pattern and continued displacement have perpetuated feelings of loss of control, which correlate with depression and anxiety.

Mental health investigators favor a recovery policy that goes even beyond long-term counseling to support organizations and initiatives that help communities rebuild themselves. Meanwhile, experts say, sending a public message that balances hope with realistic expectations for recovery is important. People need encouragement to seek professional help such as that offered by the Red Cross Access to Care program, Speier states.

And they need a reliable recovery timeline, along with simultaneous return of schools, hospitals and a justice system so they can more confidently invest in reestablishing themselves. "Most adults will be okay once they have homes and can return to normalcy," NCDP director Irwin Redlener says. "But thousands of children at critical developmental ages will now have been rootless for upward of two years, with yet incalculable consequences."

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HEALTH CALENDAR

DECEMBER

Safe Toys and Gifts Month

When buying gifts for children this holiday season, take care that they really are just fun and games. Age-inappropriate toys can pose hazards, particularly if they have parts that could lodge in a child's windpipe or eyes. Prevent Blindness America offers useful guidelines for selecting safe gifts, and the U.S. Consumer Product Safety Commission can keep you well informed about recalls and other issues.

Prevent Blindness America Safe Toy Checklist
www.preventblindness.org/children/safetoys.html

U.S. Consumer Product Safety Commission Toy Safety Publications
www.cpsc.gov/cpscpub/pubs/toy_sfy.html

DECEMBER 2–8

National Hand-Washing Awareness Week

Want to shrink your odds of catching a cold or flu this year? There's no simpler or more effective way than to wash your hands regularly. This week the Henry the Hand Foundation sets out to spread the four principles of hand awareness: wash hands when they are dirty and before eating; do not cough into your hands; do not sneeze into your hands; and, most important, do not put your hands into your eyes, nose or mouth.

Henry the Hand Foundation
www.henrythehand.com

DECEMBER 1

World AIDS Day

Although antiretroviral drugs and other medications have gone a long way toward making HIV infection more manageable—at least in the industrial world—it remains a global scourge. For the year ahead, the World AIDS Campaign is pressing a theme of "Leadership" with the slogan "Stop AIDS. Keep the Promise." Do your part by visiting the Joint United Nations Program on HIV/AIDS home page for more information. (See "Where Is the AIDS Vaccine?" on page 72.)

Joint U.N. Program on HIV/AIDS
www.unaids.org

JANUARY 2008

Birth Defects Prevention Month

Birth defects occur in about 120,000 newborns annually, and they are responsible for a fifth of all infant deaths. But expectant women can help prevent many of these problems through such simple steps as eating properly, taking the right vitamins and avoiding cigarette smoke. The National Birth Defects Prevention Network Web site has all the details that can make a lifetime of difference.

National Birth Defects Prevention Network
www.nbdpn.org

FEBRUARY

National Children's Dental Health Month

Since 1941 the annual observance of children's dental health has grown from a one-day event in Cleveland to a monthlong nationwide observance. Kits available from the American Dental Association, which include posters, handouts and other educational materials, can help local organizations plan campaigns to promote oral hygiene.

American Dental Association
www.ada.org/public/events/ncdhm/index.asp

FEBRUARY 3–9

Burn Awareness Week

Teach children how to recognize and respond to situations that can lead to fires and burn injuries, which exact an awful toll in accidental deaths and suffering every year. The British Columbia Professional Fire Fighters' Burn Fund has developed online educational safety materials suitable for kids aged five to 12 (as well as their parents and teachers).

BCPFF's Burn Awareness Week
www.burnfund.org/BAW/index.html

JOHN SLATER *Getty Images (toys)*; VICTOR HABBICK VISIONS *Photo Researchers, Inc. (AIDS)*; CORBIS *(toothbrushing)*

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EMDR: Taking a Closer Look

CAN MOVING YOUR EYES BACK AND FORTH HELP TO EASE ANXIETY?

By Scott O. Lilienfeld and Hal Arkowitz

More than 500 brands of psychotherapy exist, with new ones springing up on a nearly monthly basis. Although a handful of these neophyte treatments have been tested in scientific studies, it is anybody's guess whether the others actually work.

Over the past 15 years or so, one of these new kids on the therapy block has stood out from the pack for the remarkable attention it has received from the media, practitioners and mental health consumers. This treatment carries a mouthful of a label—eye movement desensitization and reprocessing—and it has made an impressive splash on the psychotherapy scene. Not surprisingly, most therapists refer to it simply as "EMDR," and we'll do the same here.

GETTY IMAGES

Like some other psychotherapies, EMDR was the brainchild of serendipity. One day in 1987 Francine Shapiro, a California psychologist in private practice, went for a walk in the woods. She had been preoccupied with a host of disturbing thoughts. Yet she discovered that her anxiety lifted after moving her eyes back and forth while observing her surroundings. Intrigued, Shapiro tried out variants of this procedure with her clients and found that they, too, felt better. EMDR was born.

After an initial published study in 1989, EMDR became the focus of dozens of investigations and scores of presentations at professional conferences. Shapiro initially developed EMDR to help clients overcome the anxiety associated with post-traumatic stress disorder (PTSD) and other anxiety disorders, such as phobias. Nevertheless, therapists have since extended this treatment to a host of other conditions, including depression, sexual dysfunction, schizophrenia, eating disorders, and even the psychological stress generated by cancer.

EMDR therapists ask their clients to hold the memories of anxiety-provoking stimuli—for example, the painful memories of a frightening accident—in their minds. While doing so, clients track the therapist's back-and-forth finger movements with their eyes, much like a person in an old Hollywood movie following a hypnotist's swinging pocket watch. EMDR proponents have invoked a dizzying array of explanations for the apparent effectiveness of the lateral eye movements: distraction, relaxation, synchronization of the brain's two hemispheres, and simulation of the eye movements of rapid eye movement (REM) sleep have all emerged as candidates. In conjunction with their therapists, EMDR clients also learn to replace negative thoughts (such as "I'll never get this job") with more positive thoughts (such as "I can get this job if I try hard enough").

Few psychological treatments have been as widely heralded as EMDR. Some EMDR pro-

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ponents have called it a "miracle cure" and "paradigm shift," and ABC's *20/20* proclaimed it an "exciting breakthrough" in the treatment of anxiety. More than 60,000 clinicians have undergone formal training in EMDR, and the EMDR International Association (EMDRIA), a group of mental health professionals dedicated to promoting the technique, boasts more than 4,000 members. The organization estimates that this procedure has been administered to approximately two million clients. Moreover, in some American cities, psychotherapists proudly list their certifications in EMDR on their Yellow Pages advertisements. But does it work?

The answer is not entirely straightforward. As with all psychotherapies, one can look at the question of whether EMDR "works" in several different ways. Here we will address three important variants of this question:

Does EMDR work better than doing nothing?

Yes. Numerous controlled studies show that EMDR produces more improvement than absence of treatment, at least for alleviating the symptoms of civilian PTSD, such as those triggered by rape. The evidence that pertains to EMDR's efficacy for other anxiety disorders is promising but preliminary. EMDR's effects are most marked on self-reported measures of anxiety; its impact on physiological measures linked to anxiety (such as heart rate) is less clear-cut.

Does EMDR work better than supportive listening?

Probably. Although the research evidence on this front is less extensive, most studies indicate that EMDR produces more improvement than control conditions in which therapists merely listen attentively to a client's problems but do not attempt to intervene directly. (Studies generally show, however, that such supportive listening conditions produce positive effects in their own right.) So the therapeutic effects of EMDR probably cannot be attributed entirely to the beneficial consequences of interacting with a warm and empathetic therapist. Something more seems to be going on.

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NOT A SHRED OF GOOD EVIDENCE

EXISTS THAT EMDR IS SUPERIOR TO TREATMENTS THAT THERAPISTS HAVE BEEN ADMINISTERING FOR DECADES.

Does EMDR work better than standard behavior and cognitive-behavior therapies?

No. Most behavior and cognitive-behavior therapies for anxiety rely on a core principle of change: exposure. That is, these treatments work by exposing clients repeatedly to anxiety-provoking stimuli, either in their imagination ("imaginal exposure") or in real life ("in vivo exposure"). When exposure to either type is sufficiently prolonged, clients' anxiety dissipates within and across sessions, generating improvement.

When scientists have compared EMDR with imaginal exposure, they have found few or no differences. Nor have they found that EMDR works any more rapidly than imaginal exposure. Most researchers have taken these findings to mean that EMDR's results derive from the exposure, because this treatment requires clients to visualize traumatic imagery repeatedly. Last, researchers have found scant evidence that the eye movements of EMDR are contributing anything to its effectiveness. When investigators have compared EMDR with a "fixed eye movement condition"—one in which clients keep their eyes fixed straight ahead—they have found no differences between conditions. In light of those findings, the panoply of hypotheses invoked for EMDR's eye movements appears to be "explanations in search of a phenomenon."

So, now to the bottom line: EMDR ameliorates symptoms of traumatic anxiety better than doing nothing and probably better than talking to a supportive listener. Yet not a shred of good evidence exists that EMDR is superior to exposure-based treatments that behavior and cognitive-behavior therapists have been administering routinely for decades. Paraphrasing British writer and critic Samuel Johnson, Harvard University psychologist Richard McNally nicely summed up the case for EMDR: "What is effective in EMDR is not new, and what is new is not effective." ■

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A Silent Minority

FOR SOMEBODY LIVING WITH DISABILITIES, ONE OF THE MOST INSIDIOUS HANDICAPS CAN BE A MISPLACED SENSE OF GUILT

By Kate Hooks

The Americans with Disabilities Act (ADA) is a federal civil-rights law that prohibits discrimination against people with disabilities in everyday activities, such as buying an item at a store, going to the movies, enjoying a meal at a local restaurant, exercising at a health club, or having a car serviced at a local garage.

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My mom once asked a friend why, if the ADA has existed since 1992, so much is still so inaccessible. The friend's answer was succinct: "People with disabilities comprise a silent minority."

When my mom relayed the story to me, I scoffed at the word "silent." I'm the opposite of silent. My former roommate needs earplugs to study while I talk on the phone, and my laugh is so cacophonous that entire restaurants filled with people have stopped chewing to turn and gape at me. I'm decidedly extroverted yet increasingly disabled. "Loud + Disabled = A Silent Minority?" I don't think so.

Moreover, I'm as open about my disability as possible. Short of tattooing "I have multiple sclerosis" across my forehead, I do everything I can to ensure that strangers understand why I fall over in public, why I use a wheelchair to grocery shop and why I need someone else's stool in a bar. Clearly, I have no problem discussing my disability with anyone who asks (or happens to be in the way).

But when it comes to advocacy, my mom's friend was correct: I am silent. Not only am I silent, I'm apologetic. I'm riddled with guilt whenever someone stands in the rain for an extra few moments to open a door for me or when someone in the supermarket takes an item down off the top shelf for me. I genuinely don't want to ask someone for their seat in a club, and I feel horrible asking friends to escort me to the bathroom in restaurants. I'm the only 29-year-old I know who needs assistance getting from point A to point B to guarantee that I don't wobble into a stranger, lose my balance and fall over or, most horrifying yet, injure myself in a hotel bathroom and rely on paramedics to extract me (yes, it's happened). Many times, when using my wheelchair, I get myself stuck between doors or find myself asking for help when something remains just out of my reach.

Invariably, whether I'm grabbing onto a stranger's head for balance or asking someone to open the door a little wider so I can dislodge myself from an entrance, I follow the action or re-

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quest with a guilty expression that boils down to a repetitive "I'm so sorry."

My overuse of apologies once caused my roommate to unintentionally fling me on the floor of a restaurant. While helping me to cross the room, she moved abruptly to admonish my sixth consecutive utterance of "I'm sorry" for stepping on her heels. Because my balance rested on her shoulders (burdensomely, I was convinced), I ended up under the bar.

"Sorry," according to the *Oxford American Dictionary,* denotes both regret and remorse. It's also synonymous with sadness. In all cases, the word fits my circumstance: I truly am sorry that my friends have to help me get to the bathroom; I regret my efforts to get through heavy doors with my wheelchair; I'm remorseful that I'm not able-bodied; and when I want to purchase a gift at an inaccessible store, my frustration yields a certain level of sadness. Having MS makes me mourn things I never used to appreciate: shoveling snow, vacuuming, shaving my legs without sitting on the floor of the tub, or even cleaning the toilet without fatigue. I watch my roommates take out the garbage and get ready to go out without constant concern about whether they'll be able to stand later that evening. They're able to clean the house, work out, help with my laundry and shower—all without falling over. That easy capability, to me, after a mere 10 years with MS, is remarkable.

At the same time, though, I clearly remember my disdain for such tasks: no one enjoys cleaning the toilet, fatigue or not. Which is why I feel so sorry—partially for myself (because the only thing worse than cleaning a toilet is wishing you could) but mainly for the friends and family members on whom I impose myself constantly. The unwavering love of those close to me doesn't lessen my guilt. I know my mom will still love me after she goes up and down the stairs for the fifteenth time to collect indispensable things that I've forgotten from my room, but I still feel awful.

I feel even worse when I startle strangers—when people who don't love me unconditionally have to get the Ben & Jerry's out of the freezer for me in the grocery store or when strange lifeguards at the YMCA have to scrape me off the slimy pool deck because my legs won't support me and my feet refuse to work on slippery surfaces. People have held their umbrellas over me while I struggled with my slippery metal wheelchair in the rain, have pushed me out of puddles when I was stuck, and have pulled and pushed me up stairwells. I feel like those poor people will suffer at least some level of emotional trauma as a result of having seen my tear-stained face; their lives will forever be tainted by the strange girl who lost her balance and grabbed onto them in the Gap.

Someone once wrote that as a person with a disability, you "have to be the kind of person that others want to help." For me that translates to openness about my disease, to constant apologies regarding my needs and to an overly active sense of humor—all of which compensate for my self-professed burdensome nature.

I have thought about those things a lot: whether I do, in fact, represent part of a "silent minority," why I feel so guilty and why my ex-boyfriend told me I "apologize too much." And after thinking about it and talking about it and even praying about it some, I decided that my definition of the word "silent" was limited and that my mom's friend, on some level, was right.

I view "silent" as synonymous with "quiet" (which I'm not). But "silent" also means "unvoiced" and "unspoken," which, when it comes to things I need, I am. I'm far more likely to meekly ask for help than to demand that restaurants, gas stations and other public facilities be made accessible. As my ex-roommate summed up: "You make up a population of silent people because you already feel too damn guilty about asking for help."

If the ADA's objective had been achieved (it was, after all, passed 15 years ago), I wonder, would I still need to be "the kind of person others want to help"? Would I need to apologize constantly or make sure to be open and funny and warm if I could achieve my objective without assistance? I doubt it. I'd be able to reach things in grocery stores, get jeans off the shelf in the mall and get myself through doors at the gym. I could save my overuse of "sorry" for my roommates, continue to mourn my lack of usefulness in the kitchen and help myself in public.

WOULD I NEED TO APOLOGIZE CONSTANTLY OR TO BE FUNNY AND WARM IF I COULD ACHIEVE MY OBJECTIVE WITHOUT ASSISTANCE? I DOUBT IT.

I do constitute a silent minority right now—I am careful with my energy, and I'm particular about the battles I choose. I wonder, though, when this will change; when the ADA will offer more than lip service; when it will instead provide an entire population of people with disabilities the chance to stop feeling guilty all the time and to accomplish things on their own. In the meantime, maybe it's time that I wean myself away from the phrase "I'm so sorry" and speak up about what really needs to be said. ■

KATE HOOKS is a teacher and writer based in Baltimore.

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Pro-Drug Gets Attention

FOR THOSE SUFFERING FROM ADHD, FIBROMYALGIA AND OTHER PROBLEMS, BETTER OPTIONS ARE NOW AVAILABLE

ALL-DAY RELIEF FROM ADHD:

The U.S. Food and Drug Administration is now considering whether to approve the marketing of Vyvanse (lisdexamfetamine dimesylate, made by Shire) to adults with attention-deficit hyperactivity disorder (ADHD). Shire filed for that application in June, following up on the FDA's approval of Vyvanse last February as a treatment for ADHD in children.

Like many ADHD medications, Vyvanse acts as a stimulant. (Paradoxically, stimulants can help offset such hyperactivity problems, possibly by leveling out inconsistencies in how fast different parts of patients' brains process information.) Vyvanse, however, is a "pro-drug" compound that does not exert its therapeutic effect until after the body has metabolized it. That delayed action can stretch out how long the drug works: in studies, a dose of Vyvanse was able to combat ADHD symptoms for a full day. (The delay may also make it less appealing for abuse than conventional amphetamine stimulants are.)

The review period for the adult application is 10 months; look for a decision in spring 2008.

Last June the FDA also issued an "approvable letter" to Shire for another of its pending anti-ADHD products, Intuniv (guanfacine), a once-a-day extended-release tablet. An approvable letter indicates that the FDA is prepared to approve a new drug application once certain specified conditions, such as a request for additional information, are met. According to the filed application, Intuniv, which is not a stimulant, acts specifically on the brain's prefrontal cortex to improve executive functions, such as working memory, impulse control, tolerance of frustration and regulation of attention.

MORE: www.shireadhdtreatments.com

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EASING FIBROMYALGIA: Sufferers of fibromyalgia, a painful and frustratingly mysterious affliction of the muscles and connective tissue, can finally hope for some relief. Lyrica (pregabalin, made by Pfizer) became the first FDA-approved drug treatment for fibromyalgia in June. Not all fibromyalgia patients have found that Lyrica reduced their discomfort, and common side effects have included dizziness and sleepiness. The drug had previously been approved for use in treating the nerve pain of shingles. Still more applications may yet emerge: Lyrica is also in advanced clinical trials as a treatment for epilepsy and for generalized anxiety disorder.

MORE: www.lyrica.com

NEW HOPE AGAINST RESISTANT BREAST CANCER: Ixabepilone, a compound being investigated by Bristol-Myers Squibb, shows some encouraging effectiveness against metastatic breast cancers that are resistant to three other standard chemotherapy drugs (anthracycline, taxane and capecitabine). That was the finding of a phase II clinical trial published in the *Journal of Clinical Oncology* in August. Ixabepilone belongs to a

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new class of potential chemotherapy agents called epothilones that inhibit the growth of cancer cells. In June the FDA accepted the company's New Drug application for ixabepilone, and, based on expectations, a decision should have been announced in October.
MORE: www.bms.com

NEW HIV TREATMENT: For the first time in 10 years, the FDA has approved a member of a new class of oral HIV medication. Selzentry (maraviroc, made by Pfizer) prevents HIV from entering white blood cells. The FDA granted the approval in August on an accelerated basis, after only 24 weeks of data collection during a clinical trial. The drug, however, is so far meant for use only by patients infected with a particular strain of the virus—CCR5-tropic HIV-1—that is resistant to many other antiretroviral therapies.
MORE: www.pfizer.com

LIVING WELL IS THE BEST PROVENGE? One of the most contentious and closely scrutinized decisions before the FDA concerns Provenge, a proposed therapeutic vaccine made by Dendreon for use against prostate cancer. Better options for controlling or treating prostate cancer are desperately in demand because existing treatments often fail or carry undesirable consequences (such as impotence or incontinence). A therapeutic vaccine would not be intended to prevent the disease but rather to help patients' immune systems mobilize against the cancer cells, without recourse to surgery or radiation.

An advisory panel to the FDA recommended approval of Provenge on the basis of good early clinical results, but the FDA instead requested more information last May after a second phase III clinical trial seemed more equivocal. Outraged patient groups (and investors in Dendreon) have protested this decision, at times alleging that hidden interests sabotaged the drug's approval.

Turning up the heat was a July report in the journal *Clinical Cancer Research,* which argued that clinical trials often misjudge cancer vaccines: in the case of Provenge, its failure to shrink tumors may be less significant than its success in raising survival rates. Dendreon is planning a new trial for Provenge that focuses on survival, and it could submit preliminary data from that work during 2008.
MORE: www.dendreon.com, www.provengenow.org

PULLING THE PLUG ON A NOVEL PAINKILLER: Neuromed Pharmaceuticals and Merck announced in early August that they were suspending development of a compound called MK-6721 as a treatment for chronic pain, after disappointing results in a phase II clinical trial.

MK-6721 belongs to an innovative class of analgesic compounds, called *N*-type calcium channel blockers, that block pain signals in the nervous system. It reportedly showed no adverse side effects in earlier trials, but according to the pharmaceutical makers, in the more recent tests MK-6721 lacked "the ideal pharmaceutical characteristics considered necessary" to justify further development. Nevertheless, Neuromed and Merck indicated they would continue to investigate other *N*-type calcium channel blockers for treating pain.
MORE: www.neuromed.com, www.merck.com

HEARTBURN DRUGS OKAY FOR HEART: Two studies released in May had suggested that two popular prescription heartburn drugs made by AstraZeneca, Prilosec (omeprazole) and Nexium (esomeprazole), might increase users' risks of heart problems. In August, however, the FDA concluded that the preponderance of available evidence did not support that worry and recommended that consumers continue to take the pills while investigations continued. The FDA expects to have concluded a more thorough review of the evidence by November.
MORE: www.astrazeneca.com

NEW MEDS FOR FIDO: Two recently approved veterinary drugs made by Pfizer Animal Health can help keep the family dog feeling fit.

Cerenia (maropitant citrate) is the first FDA-approved prescription medication specifically for the prevention and treatment of canine nausea. Motion sickness strikes one in six dogs during car trips and other travel. Moreover, acute vomiting from other causes is a common reason for owners to take their dogs to the vet. Unlike some other nausea remedies, Cerenia does not make dogs drowsy.

Another problem for dogs that is increasingly widespread is obesity: as many as 40 percent of American dogs are overweight, according to Pfizer. The new prescription compound Slentrol (dirlotapide) decreases dogs' appetite and food consumption: almost 98 percent of the animals in tests lowered their weight by an average of 11.8 percent. (Sorry, Garfield—Slentrol is not suitable for cats or humans.)
MORE: www.pfizerah.com

—The Editors

BETTER OPTIONS FOR TREATING

PROSTATE CANCER ARE DESPERATELY IN DEMAND BECAUSE EXISTING ONES OFTEN FAIL.

Information on new medications and approvals is presented only for general educational purposes. Decisions about taking specific drugs and selecting therapies should always be made in consultation with the appropriate medical authorities.

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THE GOAL OF BUILDING A SAFE ARTIFICIAL HEART HAS FRUSTRATED BIOENGINEERS FOR MORE THAN FOUR DECADES. AT LAST, AN END COULD BE IN SIGHT

Not Just a Pump

By Wray Herbert

In the late 1970s American television viewers were captivated by a weekly drama called *The Six Million Dollar Man,* starring Lee Majors as secret agent Steve Austin. Austin was a cyborg, a flesh-and-blood man brought back from near death and bioengineered to be superhuman in strength, speed and vision. During the series's five-year run, Austin entered the popular idiom as "the bionic man."

An era of technological optimism had been gathering momentum since the 1960s, in large part following the stunning successes of the space program. There was a growing confidence that American scientific ingenuity could engineer almost anything—including the human body. Indeed, at the same time that astronauts started flying into space, the government also set its sights on the gold ring of bioengineering: a permanent mechanical replacement for the human heart.

Fast forward to May 1988, when the *New York Times* dismissed the entire concept of an artificial human heart as the "Dracula of Medical Technology," a hubristic $240-million boondoggle. The paper's editorialists opined tersely: "The Federal project to create an implantable artificial heart is dead."

What happened? How did the grand hopes of bioengineering a human heart turn to such cynicism in just a decade?

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JAMES WORRELL

AbioCor artificial heart

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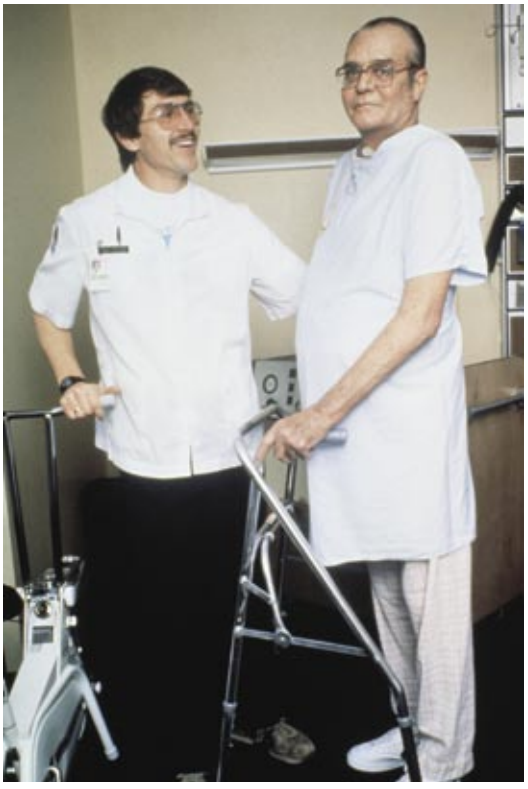
THE GOVERNMENT'S PURSUIT OF A MECHANICAL HEART WAS INSPIRED BY THE MEDICAL INADEQUACIES OF THE TIME.



Barney Clark, the first recipient of a Jarvik-7 heart, subsequently suffered a poor quality of life.

There is a long answer and a short answer to that question. The long answer is complex, encompassing several strands of basic science and technology, from materials to batteries to motors and microprocessors, plus a healthy dose of marketing psychology. The *Times* may have been premature in writing off the whole enterprise, which many believe is more promising today than ever before. Nevertheless, deconstructing the early setbacks offers a useful lens on recent progress and further challenges.

The short answer is Barney Clark.

Clark was a Seattle dentist who, in 1982, became the first recipient of a permanent mechanical heart. "Permanent" is something of a grisly misnomer, because Clark lasted only 112 days. More to the point, they were 112 miserable days for the 61-year-old, who never left the hospital and was tethered the entire time to a refrigerator-size compressor powering his noisy new heart. He suffered convulsions, cognitive problems and kidney failure, then died of massive organ failure.

The mechanical heart that kept Clark alive for those months was the so-called Jarvik-7, named after its inventor, Robert Jarvik. The nation followed Clark's progress with rapt attention, fueled by daily press conferences, which turned quickly to sympathy and disappointment as the patient deteriorated. The case was a public-relations disaster for the Jarvik-7. The quality of Clark's life with his new heart was so poor that it turned public opinion sour on the idea for a decade. Four more patients would receive permanent Jarvik-7 hearts over the next few years, and one, William Schroeder, even survived 620 days, but the damage to the dream was done. In 1990 the U.S. Food and Drug Administration withdrew permission to manufacture any more Jarvik-7 hearts.

It's easy, of course, to second-guess quarter-century-old decisions, but many cardiologists today feel that implanting the Jarvik-7 was a mistake—premature given the primitive state of knowledge at the time. Visionaries were seduced by the simplicity of the natural organ's design—which really is just a four-chambered pump—and somewhat naive about its dynamic complexity. Says Alfred Bove, vice president of the American College of Cardiology: "The God-given heart is a dynamically balanced, finely tuned organ, with the capacity to generate force, raise and lower pulse. It's not possible to get that in an artificial heart."

But it is possible to approximate it. And if nothing else, the Jarvik-7 experiments demonstrated that the basic concept was not flawed: they proved that people could survive for extended periods with a heartlike thing made of plastic and metal. Back then, that demonstration in itself was a dramatic step forward, and it was very good news for the 50,000-plus Americans with heart failure who die every year, some while awaiting one of the meager 2,200 donated hearts available for transplant. All of the work since the mid-1980s has been figuring out the problems with the Jarvik-7 and fixing them.

Robert Kung was still a young graduate student in physical chemistry when the federal government began its pursuit of an artificial heart. The Framingham (Massachusetts) Heart Study, begun in 1948, was yielding its early results on Americans' high rates of heart disease and mortality, and cardiologists were realizing just how little they understood about either the prevention or treatment of this killer disease. So in a sense, the government's pursuit of a mechanical heart was inspired by the medical inadequacies of the time.

The early target date for a fully functional artificial heart was 1972—an overly optimistic ex-

BETTMANN/CORBIS (*this page*); *Opposite page, top row, left to right:* JEFFERSON MEDICAL COLLEGE *AP Photo (Gibbon)*; BETTMANN/CORBIS (*Cooley*); MIKE SIMONS *Getty Images (Tools)*; *bottom row, left to right:* BETTMANN CORBIS (*Winchell*); TED SPIEGEL *Bettmann/Corbis (DeBakey)*; HANK MORGAN *Photo Researchers, Inc. (Jarvik-7)*; GETTY IMAGES (*AbioCor*)

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pectation, says Kung, who has spent his entire career developing a new, improved mechanical heart. He is chief scientific officer at Abiomed, a Danvers, Mass.–based company created specifically to solve the many problems that were glaringly apparent in the Jarvik-7 experiments. Even though flying rockets to the moon seems so much grander a feat, he says, it is actually much simpler because velocities and trajectories can be accurately predicted with the laws of math and physics. The interface between a mechanical heart and human tissue and blood is much more complex and squishy, involving the delicate interplay of blood-flow patterns, clotting agents, and a small army of immunological sentries and soldiers warding off infection. The heart beats, but it's not like clockwork.

This dynamism was poorly understood a generation ago, resulting in insurmountable problems. The two most daunting threats to the survival of Jarvik-7 recipients were stroke and infection. Kung, in designing a successor to the Jarvik-7 called the AbioCor, has focused on these two problems for most of three decades. The designers of the CardioWest, an iteration of the Jarvik-7 used only as a "bridge to transplant," have also been working on these problems in different ways. Here is a look at the lessons learned.

BRIAN BOHANNON

Tom Christerson holds the record so far for surviving with an AbioCor heart: 17 months, most of them spent at home.

"BLOOD WANTS TO MOVE"

William Schroeder, the longest-lived Jarvik-7 recipient, died of a stroke. It was one of the most common risks associated with the early total-heart replacements: fragments of blood cells would stick to the mechanical device, then break off, causing potentially life-threatening clots.

Part of the problem at the time was that medical scientists simply did not understand very well the physics of blood flow and the behavior of circulating platelets. As Kung says, "Blood wants to move. It wants to be in motion all the time." And when it moves too sluggishly, it will clot. On the other hand, if it moves too fast, cells can be

Timeline: Progress toward an Artificial Heart

1953 John Heysham Gibbon, Jr., performs the first open heart surgery, using a heart-lung machine that he invented. The device demonstrates that it can temporarily take the place of a living heart.

1964 The National Heart Institute (later NHLBI) sets a goal for the development of a working artificial heart by 1970.

1969 Denton Cooley replaces a patient's heart with an artificial one for three days, until a living heart is available for transplant.

1994 The Food and Drug Administration (FDA) approves the use of LVADs in heart patients awaiting transplants.

2001 Robert Tools becomes the first to receive an AbioCor, the first self-contained replacement heart. He survives for 151 days.

1950 2010

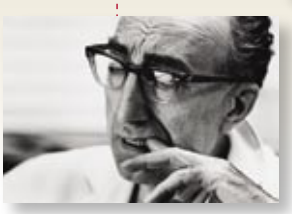
1963 Inventor Paul Winchell—better known as a ventriloquist and voice actor—receives a patent for the first artificial heart. He later donates it to the University of Utah.

1982 Robert Jarvik readies the Jarvik-7 heart, which is based in part on Winchell's original designs. It is the first artificial heart meant to serve as a permanent replacement.

1982 Barney Clark becomes the first patient to receive a Jarvik-7 artificial heart. He survives for 112 days before succumbing to clots and other complications.

2006 The FDA approves the commercial use of AbioCor hearts under a humanitarian device exemption.

1966 Michael DeBakey successfully implants a **left ventricular assist device (LVAD)** to sustain a patient for 10 days while his heart heals.



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ELIMINATING THE NEED FOR SKIN-PIERCING TUBES HAS REDUCED COMPLICATIONS FROM INFECTION.

sheared off and broken, producing debris that can glom up arteries and cause blockages.

The Jarvik-7 had a couple of fatal clotting problems that subsequent research appears to have solved. First, the materials used to build the Jarvik-7 were too coarse; they had nicks and gullies that allowed blood cells to cling and later to split off and cause problems. The AbioCor is made from titanium and a polyurethane blend called Angioflex, which is produced by a secret process that Abiomed claims makes it very pure and slick—much less susceptible to clotting.

What's more, the Jarvik-7 was powered by a large and clumsy pneumatic pump, which actually jolted the heart recipients' bodies as it forced blood through the mechanical chambers. Barney Clark's 112 days must have been extremely unpleasant, with his body constantly jostled by a clattery machine. That harsh pump has been replaced by a tiny motor-driven hydraulic one, which much more closely approximates the continuous blood flow of the natural heart and circulatory system. The rotary motor pushes hydraulic fluid from one of the AbioCor's ventricles to the other, back and forth, 100,000 times a day, pumping blood slowly but steadily to the lungs and body. A miniature electronic "controller" adjusts the flow level according to need, keeping the blood flow smooth whether a patient is sleeping or seated or strolling.

The AbioCor was in clinical trials from 2001 to 2004, during which time 14 severely ill patients received the device. All died, but it is important to know that these people were the sickest of the sick, with just weeks to live if they had had no intervention at all. A few did die of stroke, but the average survival time was more than four months, more than quadruple their life expectancy before the trial. One, Kentucky tire dealer Tom Christerson, survived 17 months and actually lived the last nine months at home with his family. Kung says that most of the clotting problems had to do with the cuffs that connect the mechanical heart to the body's circulatory system. The cuffs have since been redesigned to eliminate the clotting.

The other major killer in the early mechanical-

Continued on page 24

How the AbioCor Works

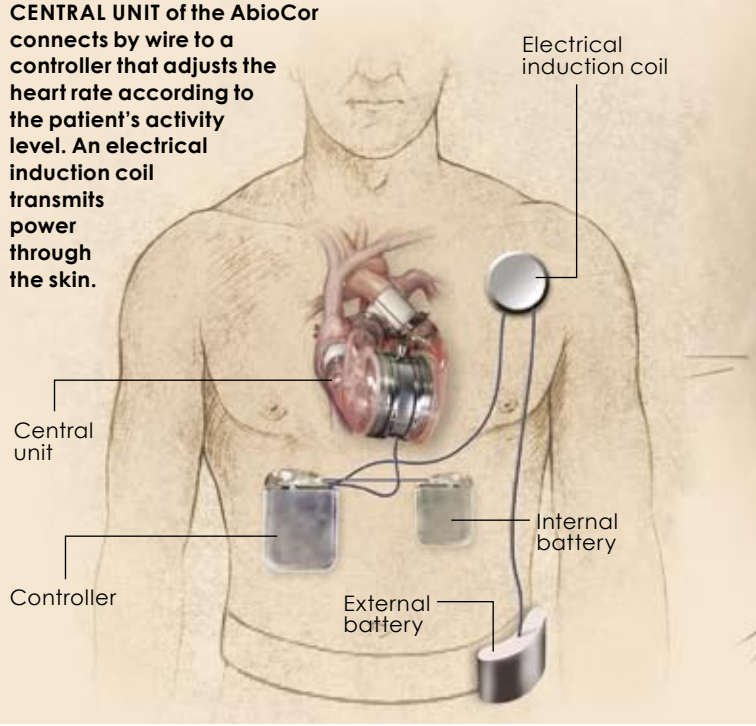
Like a human heart, the AbioCor has chambers for pumping blood on its left and right sides. Oxygenated blood from the lungs flows into and out of the left chamber, and oxygen-depleted blood from the body flows into and out of the right chamber.

At the center, an electric motor turns a miniaturized centrifugal pump at 5,000 to 9,000 rotations a minute. The pump propels a viscous hydraulic fluid; a second electric motor turns a gating valve that allows the fluid to alternately fill and empty from the two outer sections of the pumping mechanism. As fluid fills the left section, its plastic membrane bulges outward, pushing blood out of the AbioCor's left chamber. At the same time, hydraulic fluid empties from the right section and its membrane deflates, allowing blood to flow into the device's right chamber.

The AbioCor's four plastic valves are configured like natural heart valves. The inflow conduits are connected to the left and right chambers of the excised heart, called atria, and the outflow conduits are fitted to the arteries. The device weighs about one kilogram and consumes about 20 watts of power. The internal battery, electrical induction coil and controller module add another kilogram to the implanted system. Lithium-ion batteries worn on the patient's belt continuously recharge the internal battery using the induction coil. A bedside console can also be used as a power source and monitoring system. ***—Steve Ditlea***

Steve Ditlea is a New York science writer.

CENTRAL UNIT of the AbioCor connects by wire to a controller that adjusts the heart rate according to the patient's activity level. An electrical induction coil transmits power through the skin.



KEITH KASNOT

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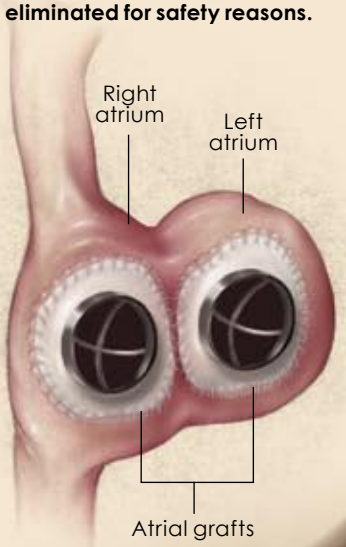
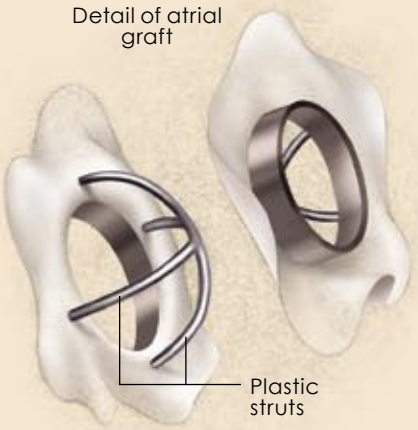
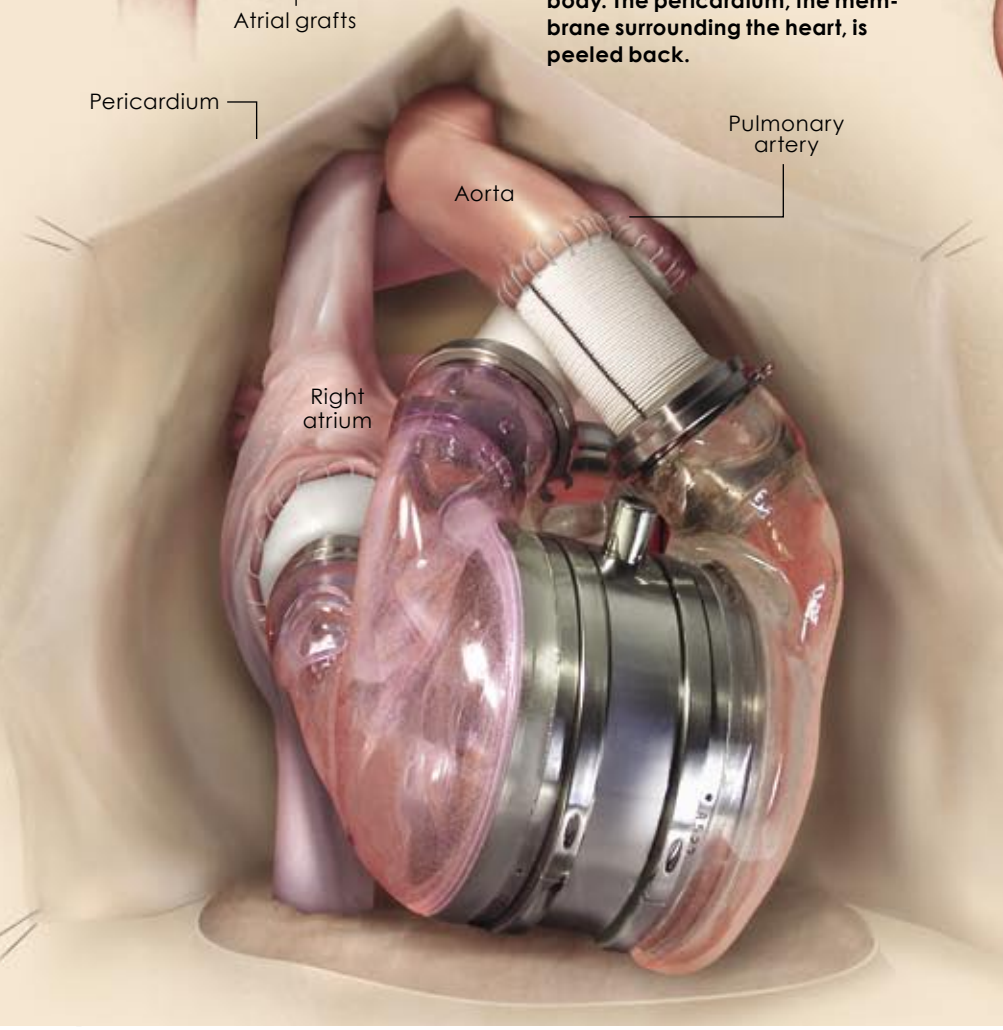
ABIOCOR attaches to the remnants of the right and left atria of the patient's excised heart. In early procedures, plastic struts helped to hold the atrial walls apart, but these were later eliminated for safety reasons.

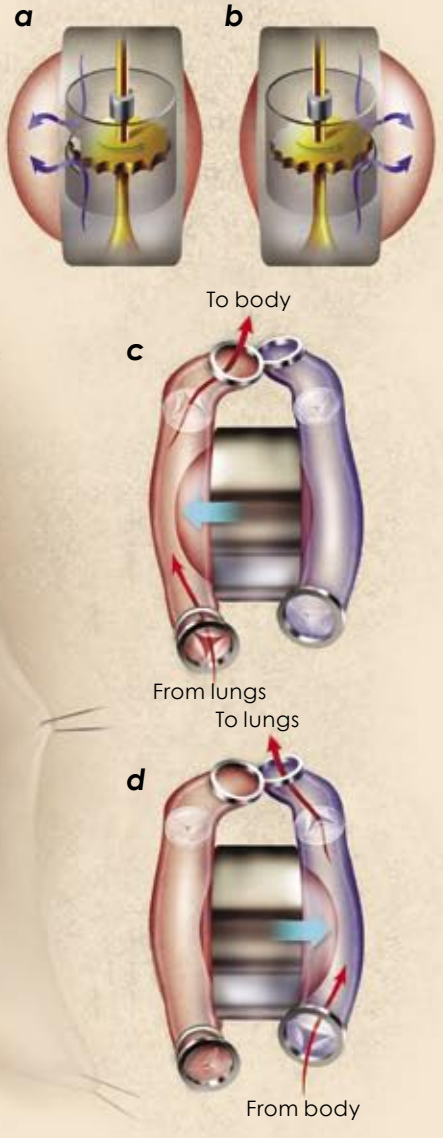




ARTIST'S RENDERING shows the AbioCor after implantation in the patient's body. The pericardium, the membrane surrounding the heart, is peeled back.



PUMPING MECHANISM of the AbioCor mimics the beating of a human heart by propelling hydraulic fluid back and forth. (The diagrams below show the device from the rear perspective.) A centrifugal pump turns continuously in one direction while a gating valve alternately shunts the hydraulic fluid to the left and right (*a* and *b*). When the fluid flows to the left, it pushes a plastic membrane into the AbioCor's left chamber, pumping oxygenated blood to the body (*c*). When the fluid flows to the right, it pushes a membrane into the right chamber, pumping oxygen-depleted blood toward the lungs (*d*).



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Restoring Flow

Doctors began implanting left ventricular assist devices (LVADs) decades ago to keep heart failure patients alive while they waited for weeks or months for an available transplant organ. Today improved designs are being installed as final fixes. Indeed, the distinction between an LVAD used as a bridge to transplant and as a permanent aid "is disappearing," says Kiyotaka Fukamachi, head of the Cleveland Clinic's Cardiovascular Dynamics Laboratory. "Some patients who received an LVAD as a bridge have been living with it for two or three years."

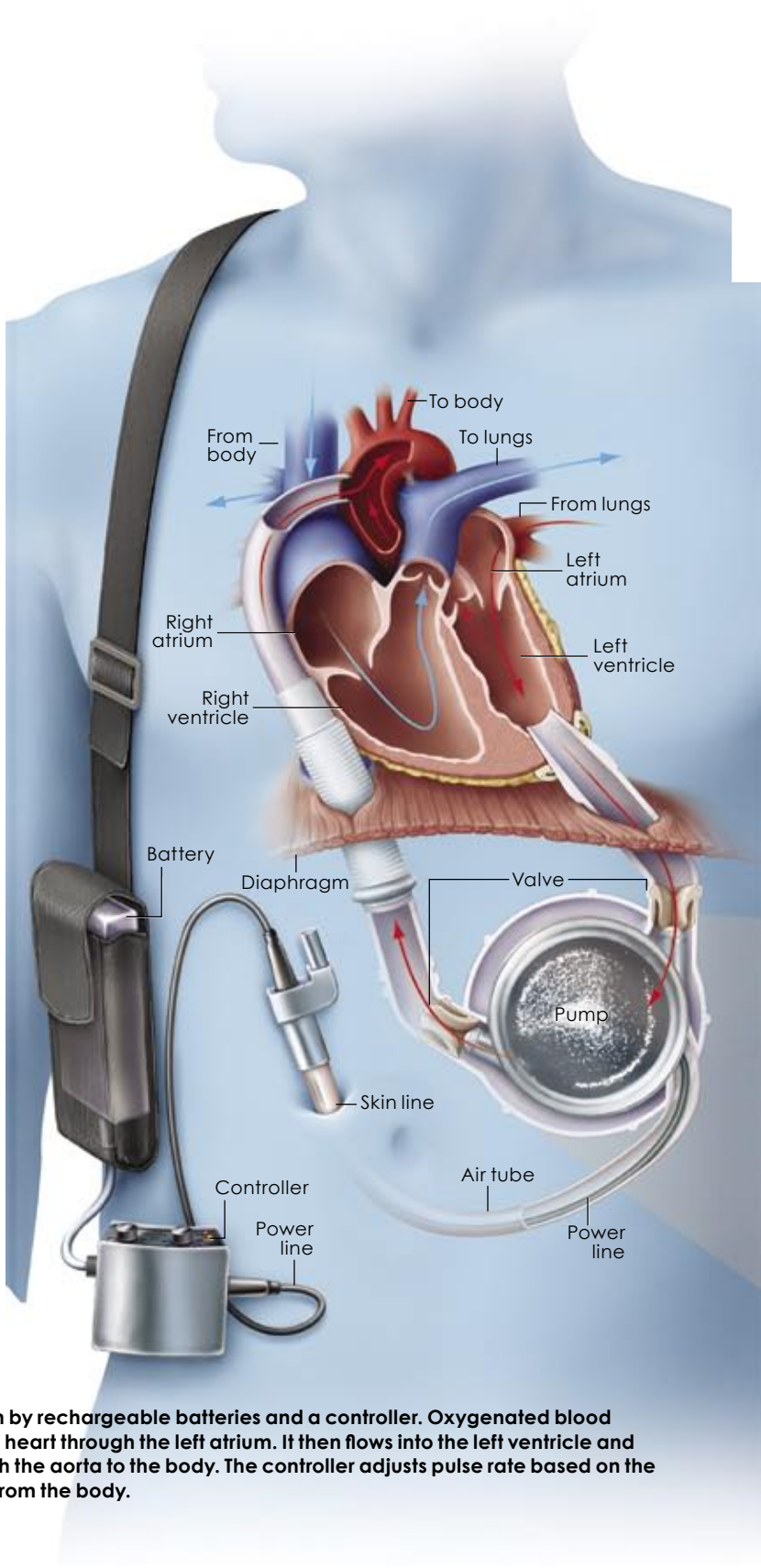
A healthy left ventricle pumps freshly oxygenated blood through the aorta to the body. LVADs help the ventricle or take over its operations if the chamber is weak or has stopped functioning. First-generation designs, which still prevail, are pulsatile: an implanted pump pushes blood in pulses like a natural heart. Second-generation LVADs are smaller, relying on a rotor that continuously streams blood. Engineers are evaluating experimental, third-generation devices that use magnetically levitated rotors, reducing moving parts.

Yet "no one approach is necessarily better than the others," Fukamachi says. "The choice depends on a patient's circumstances." The pulsatile machines, including Thoratec Corporation's HeartMate I and World Heart Corporation's Novacor, may still provide the best option if a patient needs a full takeover. Continuous-flow models such as MicroMed Cardiovascular's DeBakey can be smaller and simpler because they do not require valves or a vent tube. Levitated machines may show less wear over time. (In the U.S., HeartMate I is approved for bridge and permanent therapy; Novacor is approved for bridge. Other models are in trials.)

Complications are involved, of course. A wire must protrude from the body to a controller and batteries, leading to infection in up to 15 percent of patients. Blood clots can form inside pumps, so patients must live on anticoagulants, which increase the chance for problematic bleeding. Device failure occurs, too. But doctors are likely to implant more LVADs because heart donors remain scarce. Only 2,100 transplants are performed in the U.S. every year, whereas 3,500 to 4,000 people are perennially on the waiting list.

—Mark Fischetti

Mark Fischetti is a staff editor at Scientific American.



PULSATILE LVAD PUMP is run by rechargeable batteries and a controller. Oxygenated blood from the lungs returns to the heart through the left atrium. It then flows into the left ventricle and LVAD, which pump it through the aorta to the body. The controller adjusts pulse rate based on the amount of blood returning from the body.

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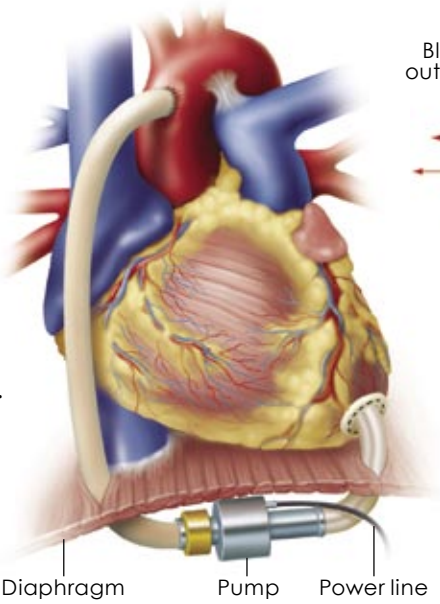
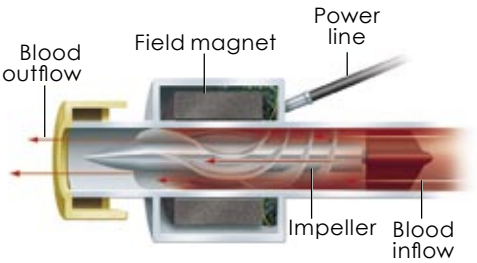
➤**RIGHT VAD, TOO:** Patients who receive LVADs often also have weak right ventricles; as many as 40 percent eventually suffer right ventricle failure. Engineers are testing right ventricular assists that could be implanted with a left ventricular assist. Kiyotaka Fukamachi's lab at the Cleveland Clinic is testing one model in animals, as are researchers elsewhere. Few designers are trying to combine both units into one, however, because that would, in effect, constitute yet another attempt at a total artificial heart.

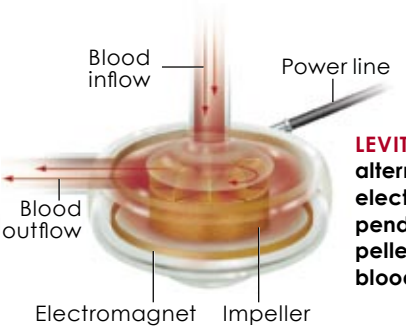
➤**LEFT OUT:** Heart failure patients may not qualify for an LVAD if they are very thin or very short, because the implanted pump can be four to six inches in diameter and the connection tubes may be five to eight inches long. (Size is one reason engineers are pursuing rotor-based devices, which can be made smaller.)

CONTINUOUS-FLOW LVAD, now in trials, has a rotor or levitated pump that circulates a continuous stream of blood through the heart's ventricles and the body's blood vessels.



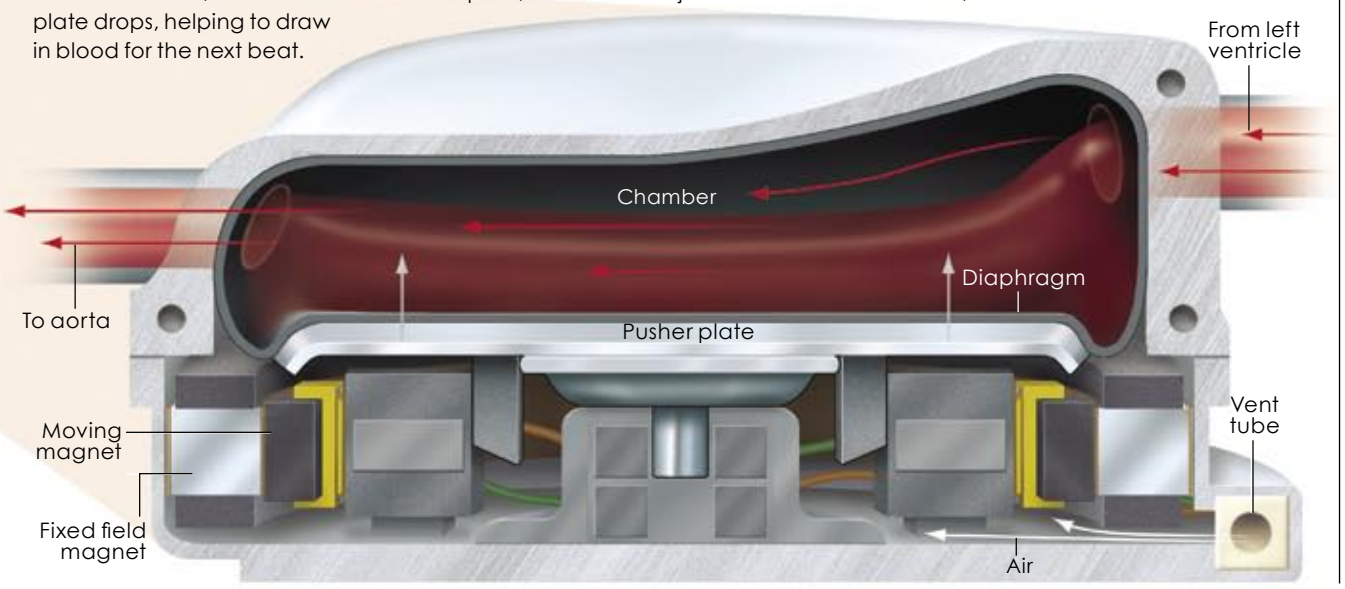


ROTOR has a stationary field magnet that pulls on magnets within the impeller's blades, spinning them.



LEVITATED PUMP is an alternative design; electromagnets suspend and spin an impeller that pushes blood through vessels.

PUMP turns magnets to drive a pusher plate upward against blood entering the chamber from the left ventricle. Air from the vent tube fills the growing void below the plate. When the chamber pressure exceeds that of the left ventricle, the inflow valve closes. Pressure continues to build until it is beyond that in the aorta; the outflow valve then opens, and blood is ejected. The air is exhausted, and the plate drops, helping to draw in blood for the next beat.



CONNIE BALEK AND KENT SNODGRASS *Precision Graphics*; SOURCES: THORATEC CORP., MICROMED CARDIOVASCULAR

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THE NATIONAL SUPPLY OF HEARTS FOR TRANSPLANTS

APPEARS TO BE STUCK AT 2,200—NOT EVEN 5 PERCENT OF WHAT IS NEEDED.

Continued from page 20

heart trials was infection. All major surgery carries infection risk, of course, and the installation of an artificial heart is a long, complicated operation. But most of the infections that plagued Jarvik-7 recipients came later, as a result of its design. The refrigerator-size pneumatic pump powered the mechanical heart through hoses, which had to run through permanent incisions in the skin. These open incisions were constantly vulnerable to infection, and in fact autopsies revealed considerable bacterial growth in the recipients following death.

The CardioWest still has problems with infection, because like its ancestor it is powered externally through large pneumatic tubes. The risk of infection has been reduced, however, by covering the tubes in a polyester fiber. The recipient's tissue intertwines itself with the fibrous surface, creating a tight fit that can keep at least some germs out. Even so, more than 70 percent of patients in a large clinical trial of the CardioWest heart did acquire infections.

HEARTMATE I PUMP, the most widely used ventricular assist device, is implanted in a patient's abdomen, as shown in this artist's rendering. Attached to a failing left ventricle, the device pumps oxygenated blood to the body.

COURTESY OF THORATEC CORP.

FIGHTING INFECTION

The AbioCor has solved the infection problem even more ingeniously. Instead of a pneumatic pump, the AbioCor uses electrical power, from either a standard outlet, an external battery or a tiny internal battery. But instead of piercing the skin, the heart's so-called transcutaneous energy transfer system, or TET, sends the energy across the skin in electromagnetic waves, from an external coil to an electromagnetically coupled internal coil, which in turn powers the heart and charges an internal battery. Eliminating the need for skin-piercing tubes has dramatically reduced complications caused by infection. Indeed, none of the 14 patients in the clinical trial died of device-related infections, according to Kung.

The TET power system has an added benefit: improved quality of life. Patients are able to power the heart's external battery while sleeping or sitting and are free to move about with a small fanny pack for a couple of hours at a time between charges. What's more, the internal battery can power the heart for about one hour, allowing patients to take showers and so forth without any external attachments. These may sound like small things, but they are a dramatic improvement over the severely restricted lives of Clark and other Jarvik-7 recipients.

The TET power system would not be possible without certain technologies that simply were not available in the early 1980s. For example, the system requires high-capacity lithium ion batteries, which are now ubiquitous in portable electronics but were not commercially available until the 1990s. The TET system also uses a very small microprocessor to regulate the energy flow. The miniaturization of electronics in general has now made this crucial design element possible.

Despite these advances in miniaturization, the AbioCor is far from small. At two pounds,

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More to Explore

- **The Total Artificial Heart: Where We Stand.** O. H. Frazier et al. in *Cardiology,* Vol. 101, Nos. 1–3, pages 117–121; 2004. A review of the AbioCor heart and its potential as an alternative to heart transplantation.
- **Mechanical Circulatory Support Therapy in Advanced Heart Failure.** Revised edition. Mario C. Deng and Yoshifumi Naka. Imperial College Press, 2007. This broad introduction to the subject of heart assist and replacement therapies covers not only the state-of-the-art technologies but also the ethical and psychological issues, with perspectives from patients as well as physicians. It is aimed at professionals in cardiology health care teams but is also accessible to lay readers.
- **The Artificial Heart page of PaulWinchell.com.** If you know actor and ventriloquist Paul Winchell only as the voice of Tigger in the *Winnie the Pooh* movies, read this excerpt from his autobiography in which he describes how he came to build the first patented artificial heart. **www.paulwinchell.com/artificialheart.htm**
- **Heart-Assist Devices page of the Texas Heart Institute.** This page from one of the institutional leaders in the development of circulatory assist devices offers links to detailed descriptions of many past and present artificial hearts and left ventricular assist devices, as well as video interviews and background information on their history. **www.texasheart.org/Research/Devices/**

the grapefruit-size device is more than twice the size of the typical human heart. That means it is too big for all children, most women, and even some grown men. Abiomed scientists are currently working on a design called the AbioCor II, which will be 30 percent smaller—small enough even for some children.

Questions remain about how much wear and tear the AbioCor and similar devices can take. No mechanical device lasts forever, and it is fair to expect some parts of this one to wear down. Cardiologist Robert Dowling, writing in the *Journal of Thoracic and Cardiovascular Surgery* during the clinical trials, estimated the life span of the hydraulic membrane—the part that expands into the ventricles to make them pump—at a year or more. The actual pump and switching valve—the only real moving parts in the heart—could last three to five years, according to Dowling. But the fact is that nobody knows for sure. All that is known is that one AbioCor heart beat inside Christerson's chest for 17 months without breakdown.

The biggest question, not only about the AbioCor but also about the larger enterprise, is how much need there is for a permanent mechanical heart. According to Timothy Baldwin of the National Heart, Blood and Lung Institute—the major funder of mechanical-heart development over the decades—government scientists gradually revised their view of heart technologies over time. While funding research on artificial replacements for full hearts, the institute was double-tracking research on various ventricular-assist devices, or VADs—devices that support left ventricle function only. The left ventricle is the strongest muscle in the heart, responsible for pumping blood throughout the body. (The right ventricle merely pumps blood to the lungs for reoxygenation.) But it is also more prone to problems. Many people suffer only left ventricular failure; their right ventricles remain healthy. With the clinical successes of the simpler devices in the 1990s, it became apparent that many people with heart failure could get by with VADs alone. But the jury is still out on this: a fair number of patients with VADs later require right ventricular support as well. Some believe that a total heart replacement, because it is better at controlling overall circulation, will lead to less kidney and liver failure.

The incidence of heart failure is on the rise, in part the result of the aging of the baby boomer generation. The national supply of human hearts for transplants appears to be stuck at about 2,200—not even 5 percent of what the population with heart failure needs. The bottom line is that for some patients, a permanent mechanical heart literally means life or death. Last fall, after the clinical trial of AbioCor, the FDA approved the mechanical heart for marketing under a special humanitarian ruling. This category of approval is reserved for devices and drugs that have proved beneficial, albeit for a very small number of patients—no more than 4,000 a year. Tom Christerson would have qualified. For him, the 17-month reprieve meant witnessing the birth of his great-granddaughter, Ellen. ■

WRAY HERBERT, who lives in Washington, D.C., writes about science and medicine and blogs about human behavior for the Association for Psychological Science at **www.psychologicalscience.org/onlyhuman/**

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Testosterone's Bad Rep

HORMONES DON'T NECESSARILY MAKE MEN VIOLENT, BUT THEY DO CAUSE THEM TO SEEK SOCIAL DOMINANCE

By Christopher Mims

Professional wrestler Chris Benoit's powerful build and muscular grappling maneuvers helped to make him a crowd favorite and propelled him to a world heavyweight championship in 2004. No one was prepared for the shocking turn this past June when he killed his wife and son, then hanged himself in their home near Atlanta. The subsequent announcement by the state medical examiner's office that Benoit's body showed he had been taking injections of testosterone (along with an antianxiety drug and a painkiller) seemed all too predictable, given how often anabolic steroids such as testosterone have been linked to violent behavior.

And yet the official findings might still have offered one surprise: according to medical examiner Kris Sperry, there was no clear evidence that the steroids played a part in the murders. Benoit's levels of testosterone were 10 times normal, but as Sperry was quoted as pointing out, "An elevation of that ratio does not translate into something abnormal in a person's thought process or behavior."

RIEDER & WALSH *Getty Images*

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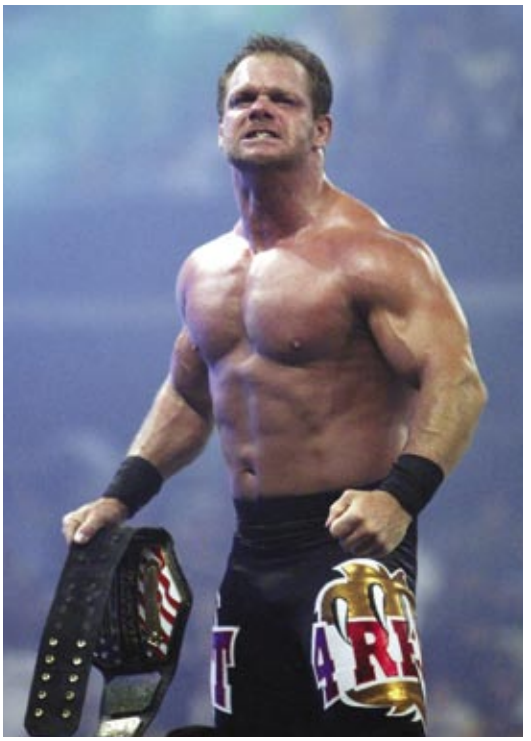


Wrestler Chris Benoit's murder of his family and his subsequent suicide were later linked to damage to his brain from concussions, not steroids.

It's commonly assumed that testosterone, that stereotypically male hormone, is intimately tied to violence. The evidence is all around us: weight lifters who overdose on anabolic steroids experience "roid rage," and castration—the removal of the main source of testosterone—has been a staple of animal husbandry for centuries.

But what is the nature of that relationship? If you give a normal man a shot of testosterone, will he turn into the Incredible Hulk? And do violent men have higher levels of testosterone than their more docile peers?

Historically, scientists had assumed the answer was yes, but the truth has proved more complex. "Researchers expected an increase in testosterone levels to inevitably lead to more aggression, and this didn't reliably occur," says Frank T. McAndrew, a professor of psychology at Knox College in Galesburg, Ill. Indeed, recent research about testosterone and aggression finds only a weak connection between the two. And when aggression is more narrowly defined as simple physical violence, the connection all but disappears.

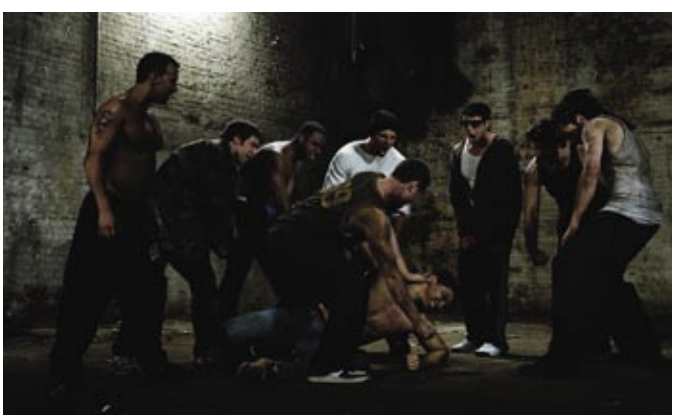
"What psychologists and psychiatrists say is that testosterone has a facilitative effect on aggression," comments Melvin J. Konner, an anthropologist at Emory University and author of *The Tangled Wing: Biological Constraints on the Human Spirit* (Owl, 2003). "You don't have a push-pull, click-click relationship where you inject testosterone and get aggressiveness."

Instead what emerges from experiments with surgical and medical castration is a more complex pattern of cause and effect. Testosterone may be necessary for enabling violent behavior, but it is not, on its own, sufficient. In that sense, testosterone is less a perpetrator and more an accomplice—one that is sometimes not too far from the scene of the crime.

In both men's and women's prisons, for example, the most violent inmates have higher levels of testosterone than their less violent peers. Yet scientists hypothesize that this violence is just one manifestation of the much more biologically and reproductively salient goal of dominance.

"It has been suggested that the antisocial behaviors related to high testosterone are a function of the manner by which dominance is maintained in these groups," says psychologist Robert Josephs of the University of Texas at Austin. In other words, if researchers were to study other groups of folks—say, the rich and famous—they might discover that testosterone is connected not to violence but to the person who drives the biggest SUV or has the nicest lawn. As Josephs puts it: "Slipping a shiv into your neighbor's back might play in the penitentiary, but it probably won't earn you any status points in Grosse Pointe."

The late psychologist James M. Dabbs made a career out of conducting studies connecting testosterone to every kind of lifestyle imaginable. In his book *Heroes, Rogues and Lovers* (McGraw-Hill, 2001), co-authored with Mary Godwin



Violent behavior among men is often attributed to excess testosterone. The truth is more complex.

WENN *Landov (top)*; ADAM WEISS *Getty Images (bottom)*

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ARE HIGH-TESTOSTERONE MALES MORE LIKELY TO BECOME VIOLENT CRIMINALS, OR DOES BEING A VIOLENT CRIMINAL RAISE A MAN'S LEVEL OF TESTOSTERONE?

Dabbs, he notes that athletes, actors, blue-collar workers and con artists tend to have higher levels of testosterone than clerks, intellectuals and administrators.

What Dabbs does not address is whether this correlation was the cause or an effect of the environment in which these men found themselves. Which is to say, are high-testosterone males more likely to become violent criminals, or does being a violent criminal raise a man's level of testosterone?

No one really knows the answer, but a growing body of evidence suggests that testosterone is as much the result of violence as its cause. Indeed, both winning a sporting match and beating an opponent at chess can boost testosterone levels. (Losing a sporting match, growing old and becoming obese all reduce levels of testosterone.)

"The causal arrow goes both ways," says anthropologist Peter B. Gray of the University of Nevada, Las Vegas, whose work shows that marriage and fatherhood lower testosterone levels. "There's evidence in humans that, just as in animals, testosterone is responsive to male-male competition."

Changes in testosterone levels in response to challenges can be further shaped by our expectations. In experiments from the 1990s that put a biological spin on the Civil War divide, psychologists Richard E. Nisbett of the University of Michigan at Ann Arbor and Dov Cohen of the University of Illinois had a volunteer "accidentally" bump into and then insult men who were raised either in the North or the South. The researchers hypothesized that Southerners come from a "culture of honor" in which aggressive responses to insults are culturally appropriate, and the results of their experiment bolstered that notion. Not only were Southerners more likely than their Northern counterparts to respond with aggression, but their levels of testosterone also rose as a result.

"From what we can tell now, testosterone is generated to prepare the body to respond to competition and challenges to one's status," McAndrew observes. "Any stimulus or event that signals either of these things can trigger an increase in testosterone levels."

That breadth of response makes sense: in the short term, testosterone helps make both males and females bigger, stronger and more energetic, all of which would be useful for winning a physical or even mental contest. Testosterone is also responsible for libido in both sexes, and if Josephs and other researchers are correct, it powers our drive for social dominance, which is one way that humans decide who gets to mate with whom.

Arguably, the weak correlation between testosterone and violence gives reason to be optimistic about the human race. Whereas other animals battle over mates as a direct result of their seasonal fluctuations in testosterone and other hormones, humans have discovered other ways to establish pecking orders. That doesn't mean we humans can't rapidly readjust our hormonal inheritance to the modern manifestations of our violent past: McAndrew's work demonstrated that one surefire way to raise a man's testosterone level is to allow him to handle a gun. ■

CHRISTOPHER MIMS is special projects editor for SciAm.com, the Web site of *Scientific American*.

More to Explore

- **Men, Honor and Murder.** Richard E. Nisbett and Dov Cohen in *Men: The Scientific Truth, Scientific American Presents,* Vol. 10, No. 2, pages 16–19; Summer 1999. The authors review their landmark research on how "cultures of honor" may shape men's violent responses to perceived slights. A link to the article in Scientific American's digital archive can be found at **www.SciAm.com/Body** or at **http://tinyurl.com/3afyyx**
- **The Tangled Wing: Biological Constraints on the Human Spirit.** Revised and updated edition. Melvin Konner. Owl Books, 2003. Konner's original edition of this book, published in 1982, became a classic for its adroit and stylishly written overview of human behavior and the biological influences on it. This second edition incorporates the intervening two decades of research.
- **The Violent Brain.** Daniel Strueber, Monika Lueck and Gerhard Roth in *Scientific American Mind,* Vol. 17, No. 6, pages 20–27; December 2006/January 2007. The authors present evidence that violent behavior results from a complex web of related factors—some genetic, some environmental. A link to the full text can be found at **www.SciAm.com/Body** or at **http://tinyurl.com/ywcnm4**

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The **Skinny** on the Environment

THE VERY STRUCTURE OF OUR COMMUNITIES MAY PREDISPOSE US TO INACTIVITY AND OBESITY. NOW RESEARCHERS ARE REMODELING CITIES FOR HEALTHIER KIDS

Well-planned communities balance natural and artificial spaces.

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JIM VECCHI *Corbis (left)*; ROY MORSCH *Corbis (above)*

by Kathryn Brown

When Susan Handy moved to Davis, Calif., in 2002, she immediately bought a commuting vehicle: a wheeled trailer, for toting her kids behind her bike. Handy, an environmental policy analyst at the University of California, and her husband frequently pedal to work, with two preschoolers in tow. Among locals, their commute is common. Fifty miles of bike lanes ribbon Davis, which is only about 10.5 square miles in area. Handy calls Davis "a small town that really works."

City planners, health researchers and local leaders want more U.S. communities to "really work"—and to that end, they have begun retrofitting the country, from Atlanta to Sacramento. Inspired by a new urbanism that celebrates neighborhoods and alarmed by health problems—particularly childhood obesity—these trailblazers are building paths, sidewalks and other architectural features while promoting policies and behaviors that get people moving.

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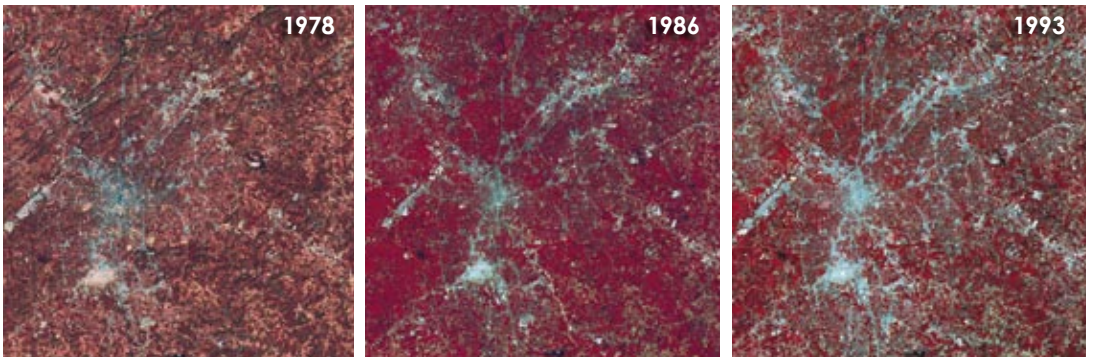

Satellite images show how much urban sprawl has grown around cities such as Atlanta (*right*). To keep themselves livable, some communities have created bike trails and other such amenities (*below*).

They have plenty to do. America's metropolitan landscape is a fractured network of residential and industrial buildings, haphazardly decorated with green space. To get around in their "built environment," or human-made surroundings, members of the average American household collectively logged more than 32,000 miles of car travel in 2001. According to National Household Travel Survey data, only 15 percent of children in the U.S. walk or bike to school—a 35 percent drop from three decades ago. At the same time, kids now spend an average of 44 hours a week sitting in front of a television, computer screen or other video monitor, according to a 2005 Kaiser Family Foundation study. Over the past five years, the study concludes, this "Generation M" (for media) has increased its total exposure by more than an hour each day, mostly by multitasking with different forms at once.

"Our built environment is a recipe for health problems, from obesity to asthma to depression," says Richard Jackson, an adjunct professor of environmental health at the University of California, Berkeley. "Poor urban design has a distinct impact." Childhood obesity, in particular, has become epidemic. Nearly a fifth of all children and adolescents in the U.S.—more than 12 million—are now overweight, according to the CDC's National Center for Health Statistics. Can the U.S. redesign itself for a healthier future?

TRAILS TO FITNESS

Today's built environments reflect decades of urban planning with a few consistent themes—cars and zoning, among them. The advent of America's car culture in the 1950s inspired suburbs that sprawl, Handy points out. Reinforcing this trend, urban zoning requirements have frequently separated industrial or commercial settings and residential neighborhoods—partly in the interest of public health, to ensure that most homeowners do not live near polluting factories.

But this blueprint currently looks less benign. Pollution from nonfactory sources, such as smog from car tailpipes and lawn equipment, still fouls the air and contributes to asthma. Idle hours in the car spent traveling between residential and commercial destinations add up to inactivity. Even those who prefer to bike or walk often confront crowded roads and hectic intersections.

Rather than simply accepting this modern metropolis, early built-environment mavericks pushed for local change. On a sunny day in 1991, for instance, three cycling buddies in sprawling Atlanta together lamented the city's polluted air and lack of bike trails. Then they got busy. The

GEORGIA TECH CENTER FOR GIS (*satellite images*); COURTESY OF PATH FOUNDATION (*trail map*)

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trio created the PATH foundation, a nonprofit whose mission is to develop a system of linked trails throughout metropolitan Atlanta.

Sixteen years later the PATH foundation has built 110 miles of trails in and around the city, through wetlands and nature preserves, along highways and across neighborhoods. The longest trail, dubbed the Silver Comet, stretches 57 miles from Atlanta to the Alabama state line. Built with a plan that combines public and private financing, all the trails are 12 feet wide, made of concrete and lined with maintained green space. PATH's executive director, Ed McBrayer, calls the trails "linear parks."

In fact, major changes in federal transportation policy are boosting built-environment projects nationwide. Spurred by local constituencies, lawmakers in 1991 and 1998 formally added bicycling and walking to transportation planning. As a result, bicycle and pedestrian projects—from sidewalks to bicycle lanes, trails and parking—now qualify for federal funds once dedicated exclusively to highways. Today states and metro areas are legally required to consider bicyclists and pedestrians in transportation plans. What's more, a 2005 federal transportation bill allocated an additional $612 million for a new national Safe Routes to School program, requiring all states to hire a coordinator to administer funds to communities for new bike lanes, pathways, sidewalks, and education and promotion campaigns in elementary and middle schools.

MORE THAN A THIRD OF CHILDREN AND ADOLESCENTS IN THE U.S.—25 MILLION—ARE NOW OVERWEIGHT OR OBESE.

"We intend for all the trails to eventually link, like a transportation system, so people can use them to get to work, school, the gym and church," McBrayer says. "We're always building: two miles there and one mile here, on abandoned railroad tracks, wherever we have the money and the political will." Although data on how the trails are used are limited, it is known that they inspire some exercise: in a January 2007 study by PATH foundation staff and Emory University researchers, sponsored by Georgia Healthcare Foundation, a third of 315 trail users surveyed at Davidson-Arabia Mountain Nature Preserve said that most of their weekly physical activity has involved the trails.

Similarly, a network of trails in the college town of Columbia, Mo., was born when educational technologist Ian Thomas and some friends calculated that the town of 75,000 included at least 60 residential streets lacking sidewalks. They founded the PedNet Coalition, now directed by Thomas, to lobby policymakers for pedestrian-friendly improvements and to promote activity to Columbia residents.

In 2004 PedNet convinced Columbia's city council to revise its street design standards, adding or widening sidewalks, bike lanes and mixed-use paths. Those changes, in turn, helped the city win a $25-million grant from the Federal Highway Administration to build a comprehensive cycling and walking network. As part of the grant, Columbia will document how its efforts boost bicycling and walking, reduce traffic and energy use, and promote better health and a cleaner environment.

AGE FOTOSTOCK

Bicycling to work is one way to fight back against the environmental forces that discourage exercise.

Built-environment advocates agree that promotion—from generating political will to inspiring individual choice—is critical to their cause. Thomas points to school location as one example. "Because public schools are not seen as high priority, they are underfunded and thus buy the cheapest land available, on the edge of town," Thomas explains. "How do you get your kids there? You have to drive."

Even the support of neighbors isn't guar-

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Encouraging children to enjoy the outdoors is beneficial for them and, in the long run, for the environment.

TOM AND DEE ANN MCCARTHY *Corbis (top)*; COURTESY OF DAN BURDEN *(bottom)*

anteed. In Atlanta, McBrayer was surprised to discover that culture—not just cash—was an obstacle. "I initially assumed everyone wanted to be connected," McBrayer recalls. "And that's not true. There are class and race issues, privacy issues and people who don't want things to change."

Adding to the challenge, Americans plainly enjoy their cars. In a 2005 study sponsored by the Southwest Region University Transportation Center, Handy and her colleagues interviewed Texas drivers to determine their routes to local destinations. They asked the question: How much of driving is determined by choice, rather than need? The answer: a significant amount. The study found that people often take extra trips, choose longer routes, pick more distant destinations and opt to drive rather than walk or bike.

Exercise physiologist Russell Pate of the University of South Carolina sees this tendency in his own community. "I live in a safe, relatively low traffic neighborhood with sidewalks that lead to a local elementary school," Pate says. "Every morning there's a line of SUVs half a mile long dropping off kids. The built environment is not the barrier there."

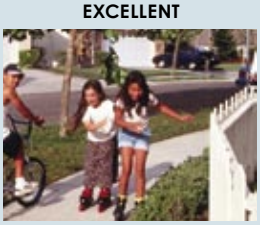
DESPERATION GROWS

Yet as the health-environment connection evolves into a national issue, foundations are stepping up to the challenge. This year the Robert Wood Johnson Foundation (RWJF), the largest U.S. philanthropy devoted to health, committed $500 million to fighting childhood obesity. Those funds will in part support three existing RWJF organizations—Active Living by Design, Active Living Research and Leadership for Healthy Communities—that seek to change policy, the environment and behavior to boost physical activity.

"There's almost a desperation around the country to do something about childhood obe-

Voting with Their Feet

What makes a community pedestrian-friendly? The Florida-based nonprofit organization Walkable Communities promotes principles that can help cities, towns or even just neighborhoods become more comfortably and safely conducive to foot traffic. It also rates instances of those environments on a scale from "exemplary" to "hall of shame." More information and examples of good community design can be found at www.walkable.org ***—The Editors***

	EXEMPLARY	EXCELLENT	GOOD	FAIR
SIDEWALKS They tend to become more "walkable" as they get wider and should never be less than five feet across. Attractive buffers between sidewalks and streets are important. Curbing that impedes cars from accidentally mounting sidewalks is important for safety.				
MAIN STREETS Walkways on main streets should be wide and attractive and flanked by many shops and residential buildings. Activities should keep the sidewalks in use as often as possible. Well-maintained benches and good lighting are essential.				

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The Spectrum of Moderate Exercise

Getting exercise doesn't have to mean getting anywhere near a gym. Even fairly sedate activities, if done regularly, can burn calories and contribute to fitness (*below*). Find chores or sports appropriate to your energy and available time (*right*) and do them routinely. Even casual chores can burn off extra calories if you do them long enough as part of a regimen.

—The Editors

Activity	Calories burned per 30 minutes
Walking (leisurely), 2 miles per hour	85
Walking (briskly), 4 miles per hour	170
Gardening	135
Raking leaves	145
Dancing	190
Bicycling (leisurely), 10 miles per hour	205

SOURCE: National Heart, Lung, and Blood Institute (www.nhlbi.nih.gov/health/public/heart/obesity/wecan/)

Examples of moderate amounts of physical activity

Common Chores	Less Vigorous More Time	Sporting Activities
Washing and waxing a car for 45–60 minutes		Playing volleyball for 45–60 minutes
Washing windows or floors for 45–60 minutes		Playing touch football for 45 minutes
Gardening for 30–45 minutes		Walking 1.75 miles in 35 minutes (20-minute mile)
Wheeling self in wheelchair for 30–40 minutes		Basketball (shooting baskets) for 30 minutes
Pushing a stroller 1.5 miles in 30 minutes		Bicycling 5 miles in 30 minutes
Raking leaves for 30 minutes		Dancing fast (social) for 30 minutes
Walking 2 miles in 30 minutes (15-minute mile)		Water aerobics for 30 minutes
Shoveling snow for 15 minutes		Swimming laps for 20 minutes
Stair climbing for 15 minutes	More Vigorous Less Time	Basketball (playing game) for 15–20 minutes
		Bicycling 4 miles in 15 minutes
		Jumping rope for 15 minutes
		Running 1.5 miles in 15 minutes (10-minute mile)

sity," says Active Living Research program director James Sallis, who is also a psychologist at San Diego State University. Active Living Research, in particular, is working to assemble evidence that the right built environments boost physical activity and improve health. "Increasingly, we plan to focus on funding peer-reviewed research that documents the most promising ways to reduce childhood obesity," Sallis says.

In one of his own studies, published this past March in the *American Journal of Health Promotion*, Sallis collaborated with urban design specialist Lawrence Frank of the University of British Columbia and others to link Atlanta's built environment with walking patterns in the city. Surveying more than 3,000 children and their parents, the researchers found that kids aged 12 to 15 were three times more likely to walk half a mile a day if a park, store or other popular destination were located within about 0.62 mile (one kilometer) of their homes. Overall, the team reported, children and families liv-

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ing in a "mixed-use" community—which offers destinations within walking distance—walk significantly more.

Walking half a mile may not sound like much exercise, but Pate puts it into perspective. He notes that preventing excess weight gain is likely to be easier than losing pounds. Furthermore, he says, most people pack on pounds gradually, because their day-to-day consumption of unburned calories is relatively small. Over time, for instance, 50 extra calories a day can cause someone to become overweight. And "a 10-year-old can burn more than 50 calories just walking to or from school or the park on a daily basis," Pate points out.

Still, skeptics question how much sprawl is to blame for obesity. In a 2003 online editorial, the Heritage Foundation, a conservative think tank in Washington, D.C., argued that without more evidence, public policy should not require denser, mixed-use community designs. The foundation emphasized that data from the CDC on 445 counties showed few overall weight differences between communities designed differently. "For the country as a whole and comparing citizen weight in the 25 counties at either extreme of sprawl and compactness, 19.2 percent of residents in the least sprawling communities were obese, while 21.2 percent in the most sprawling were obese," the editorial noted, calling such differences "trivial."

Sallis has heard that argument before. "Most people would agree that there is not going to be a single solution to childhood obesity," he responds. "We have to pursue many solutions. We have to make it harder to drive and easier to bike. We have to make it easier to find affordable, healthy food and harder to find junk food. We have to make it easier for kids to be active at school and after school. Obesity is a difficult problem to fix, but it's certainly possible—and environment is a factor."

In particular, Sallis continues, minority and

Reconnecting Kids with the Outdoors

Researchers who study obesity can calculate calories, measure weight and, over time, convincingly link the two. That straightforward equation supports a simple argument for altering the built environment to get children moving. But could a less clinical connection with nature be equally important? Across the nation, researchers, environmentalists and political leaders are sounding the alarm over a nonmedical condition dubbed "nature-deficit disorder."

S. KUTTIG *plainpicture/Corbis*

In a popular 2006 book, *Last Child in the Woods*, journalist Richard Louv coined the term, which he defined as a critical disconnect between children and nature. The book lamented this fundamental loss—and its social, psychological and even political implications. As kids spend fewer hours exploring, playing or just poking around outdoors, Louv argued, they lose creativity, a sense of belonging and an appreciation for the world around them.

Nature's broad health value has not been rigorously studied, partly because it is difficult to evaluate clinically, notes Richard Jackson, an adjunct professor of environmental health at the University of California, Berkeley, and former director of the National Center for Environmental Health at the Centers for Disease Control and Prevention. But, he argues, that snag shouldn't slow efforts to address the situation. "The tragedy is that we removed nature from children's lives without the benefit of a randomized, controlled clinical trial, so why would we need trials to restore childhood?" Jackson says.

Indeed, governmental organizations are already springing into action. Connecticut Governor M. Jodi Rell, for instance, recently launched "No Child Left Inside," an initiative to inspire families in his state to explore the outdoors. The Texas Parks and Wildlife Department has rolled out "Life's Better Outside," a similar public awareness campaign. ***—K.B.***

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"Obesity is a difficult problem to fix, but it's certainly possible—and environment is a factor." —*James Sallis*

Davis, Calif., is a relatively small community, but it features 50 miles of bike trails, which contribute to the overall quality of life.

COURTESY OF THE CITY OF DAVIS, CALIF.

low-income communities need new solutions. Studies have shown that these neighborhoods, on average, include fewer parks, more fast food outlets and more crime than affluent or Caucasian neighborhoods. Against this backdrop, these communities frequently suffer higher rates of obesity. Active Living Research plans to increase its support for reviews of these high-risk populations, Sallis says.

Other investigators are evaluating classic neighborhood designs. In northern California, Handy and her colleagues are studying cul-de-sacs, those horseshoe-shaped streets that typically dead-end at middle-class family homes dressed with basketball hoops, soccer nets and other sports paraphernalia. Seeking more "connectivity," partly to promote walking and biking, city planners are increasingly outlawing cul-de-sacs in favor of streets laid out in a grid pattern.

But in a study presented at an Active Living Research Conference this past February, Handy's team reported another side to the story. Across 27 households in Woodland, Calif., 75 percent of children living in cul-de-sacs reported being highly active outdoors, versus 55 percent of those residing on through streets. In a related survey of 1,672 parents, children ages five to 12 living in cul-de-sacs played outside more than four times in a given week, at least once more than those on through streets. "What's the best neighborhood design for kids, and what's the best for adults?" Handy asks. "The answer may not be simple."

Elusive or not, the built environment is likely to become an even hotter topic of debate in years to come. For proof, Jackson points to his experience at U.C. Berkeley. "My students are as intensely invested in these issues as students were 30 years ago in the Vietnam War," he says. "We're going to retrofit communities to improve our health—and to improve our environment. These concerns are here to stay." ■

KATHRYN BROWN, a science writer, is also vice president of marketing and communications at the Conservation Fund, an environmental nonprofit organization in Arlington, Va.

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Getting to Know Nutraceuticals

CLAIMS FOR SOME OF THESE FOOD-BASED DIETARY SUPPLEMENTS STAND UP TO SCIENTIFIC SCRUTINY, BUT OTHERS FALTER

By Thomas Hayden

We live in an age when good nutrition practices—eat lots of whole grains, fresh fruits and fresh vegetables; hold the fatty meat and hydrogenated vegetable oils—are simple, straightforward and widely available. But visit a well-stocked health food store, pharmacy or supermarket, and you'd never know it. The variety of dietary supplements can be overwhelming, with dozens of vitamins, minerals and extracts offered alone and in combinations targeted at every possible intersection of age, sex and activity. And that selection is a nutritional desert compared to the tropical rain forest–level diversity of supplements at more specialized stores.

Dietary supplements are big business in the U.S.: consumer sales in 2006 were estimated at $22.5 billion, with some 60 percent of Americans taking at least a daily multivitamin. But thanks to a regulatory structure designed more to promote the availability of supplements than to ensure that they deliver on their promises, it can seem impossible to figure out what—if anything—you should be taking. The options range from the almost appetizing juxtaposition of garlic, cranberry and soy concentrates to the downright macabre "glandulars." And if cramming pituitary, prostate and pancreas extracts into a single pill doesn't count as overkill, then surely another product containing vitamins, minerals *and* most of the biochemical intermediates of the cellular Krebs cycle must. The skeptical browser could be tempted to ask where to find the snake oil aisle.

But whereas some, or perhaps many, nostrums are no more likely to improve longevity, alertness and athletic performance than the cure-alls of old were to ward off dropsy or nervous agitation, not all can be so easily dismissed. Several once exotic dietary supplements have been the focus of investigation for more than a decade now, and a select few can boast strong quantitative support as a result. One group in particular, the nutraceuticals, is attracting the attention of health advocates and scientists alike.

Occupying a space somewhere between

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Omega-3 fatty acids from cold-water fish can help prevent heart attacks and cardiac deaths, but their value for preventing strokes is much murkier.

OMEGA-3s

essential nutrients (those nutrients critical to normal health, such as vitamins) and drugs with defined impacts on specific diseases, nutraceuticals are bioactive chemicals derived from foods but taken as supplements at much higher concentrations than diet alone could provide. They include antioxidants from fruits and berries, fatty acids found in cold-water fish, and potentially disease-fighting compounds from common spices such as cinnamon and turmeric. Claims have been made for their role in everything from fighting cancer and cardiovascular disease to maddeningly vague notions about "supporting healthy living."

"The category of nutraceuticals is really very broad, and their effects may be subtle," says Paul M. Coates, director of the Office of Dietary Supplements (ODS) at the National Institutes of Health. "That gives you a clue to the scientific challenges of understanding them. They range from supplements where we don't even know what the active ingredients are to compounds that are well characterized chemically but where the mode of action is still unknown."

To date, most nutraceuticals have been the subject more of marketing hype than of methodical clinical testing, and for many, it is not even yet known whether they provide more benefits than risks for consumers. But in at least a handful of cases, the science is starting to catch up with the health claims.

THE FISHY BENEFIT OF OMEGA-3s

Probably the best known of the nutraceuticals, the omega-3 fatty acids, are also the most intensively studied. Like all fatty acids, the building blocks of fats and oils, omega-3s are linear molecules with a carboxylic acid "head" at one end trailing a "tail" of linked carbon atoms. Those links can be made with either single (saturated) or double (unsaturated) chemical bonds. "Omega-3" simply refers to a double bond in the third position from the end of the carbon tail. Starting with alpha-linolenic acid (ALA, an essential nutrient common in many nuts and vegetable oils), our bodies can synthesize all the omega-3 fatty acids they need to build cell membranes and carry out a host of cellular functions.

But evidently we could stand to make a lot more of at least a couple of them. Beginning in the 1970s, epidemiologists started to notice that Eskimo and other groups of people who ate a lot of cold-water fish tended to have low levels of heart disease and stroke. Oil from such fish is packed with two unusually long omega-3s, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).

"The epidemiological evidence was strong enough that it led to a whole series of clinical studies and randomized control trials with fish oil," says nutritionist Penny M. Kris-Etherton of Pennsylvania State University. By 2002 the results were positive enough for the American Heart Association panel on which Kris-Etherton sat to issue a statement recommending increased fish consumption for the general public and daily consumption or supplements of fish oil for coronary heart disease patients. Since then, Kris-Etherton says, "the evidence has just grown stronger for a cardioprotective effect from marine-derived omega-3 fatty acids."

Stronger, yes, though not necessarily less complicated. In a 2006 review of 842 scientific papers on omega-3 fatty acids and cardiovascular disease, a research team based at the Tufts–New England Medical Center in Boston concluded that only EPA and DHA seemed beneficial—ALA, their plant-produced precursor, was not. And while the studies showed clear evidence that fish oil helped to prevent heart attacks and cardiac deaths, especially among patients who had already suffered one heart attack, the effects on stroke were all over the map. For people who have pacemakers, too, "there is a mixed bag of evidence," Kris-Etherton says. "One study shows a benefit, one shows an adverse effect and one shows no benefit." It is a common issue with nutrition studies, she notes—given the vast diversity of human research subjects, variations in the

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concentration or mixture of supplements, and often uncontrolled factors such as baseline diets or preexisting illnesses, "it's not unusual to see different studies canceling each other out."

Understanding exactly how DHA and EPA work would help, but the molecular pathways underlying the fatty acids' heart-protective activity are still unknown. They seem to lower blood levels of triacylglycerol (often called triglyceride), keep cholesterol from gumming up arterial walls, and help to control unwanted blood clotting and inflammation, among other risk factors. Given that fish oil has now been linked to improvements in everything from asthma and rheumatoid arthritis to type 2 diabetes and neurological diseases, there is almost certainly more than one molecular mechanism in play and almost certainly a bright future for omega-3 fatty acids on the supplement shelf.

SCIENCE SOURS ON FAVORITES

The outlook is not quite so rosy for all the early candidates for nutraceutical stardom, however. In many ways, lycopene was a food manufacturer's dream compound. Grocery profit margins are notoriously slim, and adding nutraceuticals to staple foods has been prohibitive: consumers who will pay $20 for a bottle of fish oil pills balk at shelling out an additional dollar for a loaf of bread supercharged with omega-3 fatty acids. But lycopene, a deep-red plant pigment and powerful antioxidant, not only shows up in plants such as tomatoes for free, its bioavailability is actually increased by the boiling, squeezing and other rigors of food processing.

Early epidemiological studies suggested that men who ate diets rich in tomato products enjoyed lower than average rates of prostate cancer, and lycopene was identified as the likely reason. The ironic result is that while ketchup may not be the school lunch "vegetable" President Ronald Reagan once claimed it to be, for a while even a foil packet of the stuff had a legitimate shot at being declared a dietary supplement.

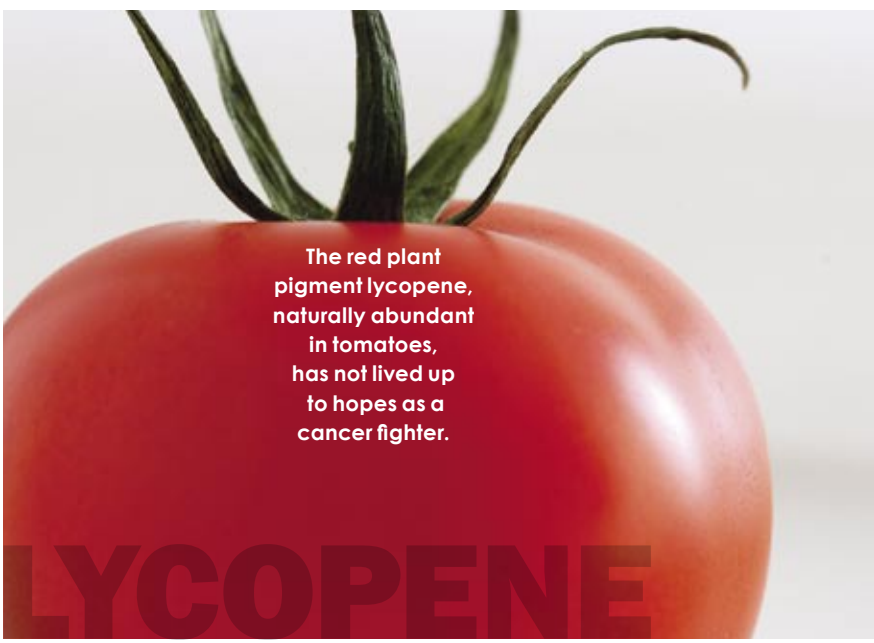
Ulrike Peters isn't happy that she had a hand in placing ketchup back in the condiment aisle. A nutrition and genetics epidemiologist at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle, she had high hopes for lycopene's cancer-fighting ability.

But when her research team analyzed blood lycopene levels of participants in a large cancer study, including 692 men who had developed prostate cancer and 844 randomly selected men who had not, they found no association between the antioxidant and the malignancy. Even more troubling, her study found a link between high blood levels of lycopene's chemical cousin, beta-carotene, and an *increased* risk of aggressive prostate cancer—not enough to justify avoiding carrots and other food sources of beta-carotene but an ominous sign that not all food-derived compounds are necessarily benign when taken at higher doses.

"The results were very disappointing," Peters says. "It would be great to have such an inexpensive way to lower prostate cancer risk, but our study dampens that possibility. Unfortunately, it often happens that health claims get out in front of scientific evidence."

Whether that has also been the case with another, much more popular supplement is still unclear. Glucosamine, a simple amino sugar, is well known to biochemists as the precursor for a wide range of important structural components of the body, including the protein collagen in tough connective tissues such as tendons and ligaments. Collagen is also a major component of the cartilage that makes up the smooth layer that protects and lubricates the bones in joints. Early observational studies suggested that glucosamine could be help-

THE OUTLOOK IS NOT SO ROSY
FOR ALL THE EARLY CANDIDATES FOR NUTRACEUTICAL STARDOM.



The red plant pigment lycopene, naturally abundant in tomatoes, has not lived up to hopes as a cancer fighter.

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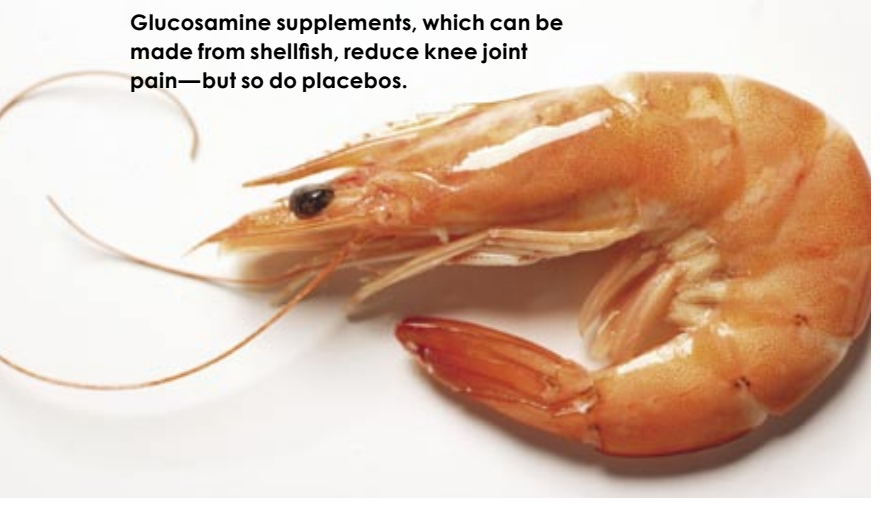
EARLY OBSERVATIONAL STUDIES SUGGESTED THAT GLUCOSAMINE COULD BE HELPFUL IN COMBATING OSTEOARTHRITIS.

ful in combating the pain and cartilage destruction of osteoarthritis, and it is widely available as a supplement derived from shellfish, often in combination with the biochemicals chondroitin sulfate, which helps to make collagen spongy, and methylsulfonylmethane (MSM), a potential anti-inflammatory agent.

Consumer sales reached an estimated $818 million for glucosamine and chondroitin sulfate in 2006, according to the *Nutrition Business Journal*. Observational studies, while sometimes contradictory, have suggested that arthritis sufferers do indeed benefit from using the supplements. That possibility led to a large NIH-funded clinical trial of the supplements involving patients with knee osteoarthritis. For 24 weeks, 1,583 participants in the aptly named GAIT (Glucosamine/chondroitin Arthritis Intervention Trial) were given one of the following treatments: glucosamine, chondroitin sulfate, both in combination, a placebo, or the COX-2 inhibitor Celebrex (celecoxib) as a control. (COX-2 inhibitors have since been linked to negative cardiovascular side effects.)

The results, published in 2006, were underwhelming. True, almost 67 percent of the patients taking glucosamine plus chondroitin sulfate reported a significant decrease in knee pain—but so did fully 60 percent of those taking the placebo. Only in patients with moderate or severe knee pain at the outset did the supplements show a significant advantage over the placebo, with almost 80 percent of that group reporting a significant improvement, compared with 54.3 percent who took the inert pills. That favorable result is nothing to sneeze at—nor, for that matter, is a placebo effect of 60 percent—but it's far from warranting a blanket recommendation.

GLUCOSAMINE



Glucosamine supplements, which can be made from shellfish, reduce knee joint pain—but so do placebos.

AGE FOTOSTOCK

SIMPLE FOODS AREN'T SO SIMPLE

Even if ketchup is one day recognized as a nutritional powerhouse, it's not likely to topple tofu from its shimmering, gelatinous perch atop the health food heap. High in protein and low in sugars and unhealthy fats, soybeans and the bean curd produced from them have long been lauded as a sound substitute for animal proteins. But they are also loaded with bioactive compounds, and the science is not yet in on whether consuming them at nutraceutical doses is a good or bad thing. The most investigated of those are a group of hormonelike polyphenols called isoflavones, which seem to have effects on everything from kidney and cardiovascular disease and various cancers to hot flashes, bone calcium loss and other symptoms of menopause.

Connie Weaver, a Purdue University nutritionist and director of that institution's Botanicals Research Center for Age Related Diseases, first became interested in soy isoflavones in 1999. "I went to a local health food store," she recalls, "and there were 13 different supplements that claimed to be effective for bone loss." But when she checked the research, Weaver recalls, "the literature was pathetic. I decided we'd better start doing some studies."

What she and other researchers have found is a vast swamp of complexity. Of the two main isoflavones, genistein and diadzein, the former seems to be more effective in preventing osteoporosis. Unless, that is, the person consuming it happens to have bacteria in the gut that convert the compound diadzein into another one called equol, which might offer more bone protection than either of the soy isoflavones—or might not. And there's even some worry that the soy compounds could boost rates of breast cancer, just as estrogen supplements used in hormone replacement therapy can.

"Nutritionally you've got to appreciate soy," Weaver says, "but there are also all these bioactive substances in there." At high concentrations,

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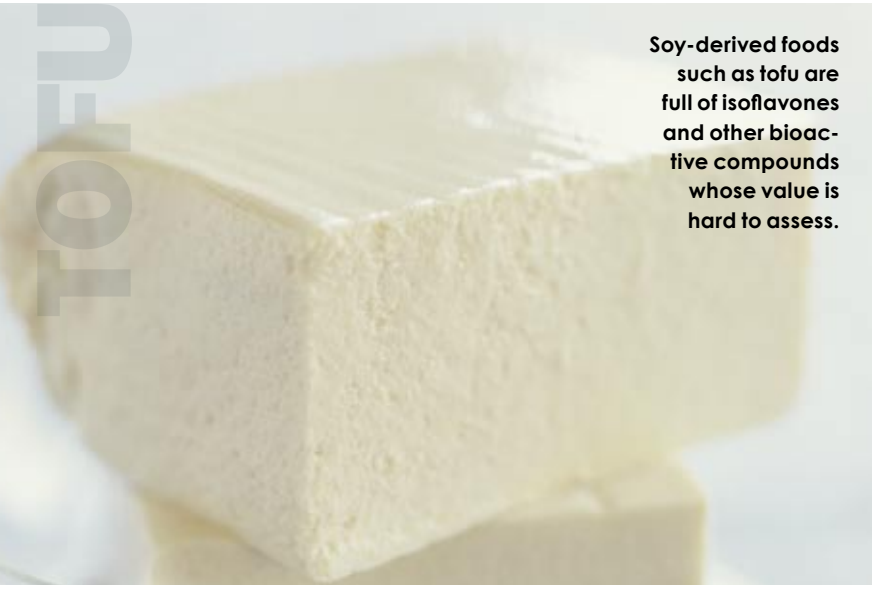

Soy-derived foods such as tofu are full of isoflavones and other bioactive compounds whose value is hard to assess.

she adds, "the problem is that they do some good things, some other things, and some who-knows-what things." The goal, Weaver asserts, "is to figure out what combinations have advantageous impacts on bone health, heart health, and so on, without deleterious impacts." At least three long-term trials testing the effects of soy isoflavones on bone health are in progress, Weaver notes, "but we've got a long way to go before we can say what works and what doesn't."

That conclusion means more research, of course, and dozens of nutraceutical trials are under way, many sponsored by ODS and other branches of the NIH. But some investigators fret that vital studies are being rushed or overlooked because of limited research funding. Peters worries that lycopene's lackluster performance to date may mean that it never progresses to clinical trials—a situation that could leave millions of consumers paying for supplements that might not be doing them any good. "We can't recommend using lycopene based on the current evidence," Peters says, "but that doesn't mean it has no benefit. There are some important studies that haven't yet been done."

Similarly, Greg M. Cole, a researcher at the University of California, Los Angeles, who sees great promise in using omega-3 fatty acids to prevent Alzheimer's disease and other forms of age-related dementia, expresses concern that current clinical trials lack funding to target the most promising patient population—people who have not yet started to show signs of those problems. "The risk of Alzheimer's doubles with every five years after age 65," he says, "and we've got a generation of 75 million people heading into that. We can't afford to miss something that might help with prevention just because we couldn't find the money to study it."

NOT-SO-HELPFUL GUIDELINES

In the meantime, patients, physicians and just plain folks will have to do the best they can to make smart choices with incomplete and potentially misleading information. The oversight of dietary supplements is loose: FDA regulations allow for several different types of efficacy claims to be made on labels, including fairly robust "significant scientific agreement" claims that the nutrient in question has a direct effect on a specific disease, but also so-called qualified health claims, where phrases such as "some evidence suggests that" are added. There's even room for "structure/function" claims: "calcium builds strong bones" is a noncontroversial example—which are not even evaluated by the FDA. (The claims do have to carry a footnoted disclaimer to that effect, however, a stipulation that can result in supplement labels with more asterisks than a Major League Baseball record book.)

"The danger of pseudoscience and quackery is very real," says Jeffrey I. Mechanick, an endocrinologist at the Mount Sinai School of Medicine who has written extensively about the use of dietary supplements in the treatment of diabetes and other metabolic diseases. "Dietary supplements in general should not be supplanting proven therapies," he cautions, "but I don't see any reason to use words like 'alternative' or 'complementary' to describe them. I just use 'proven' or 'unproven,' and that proof is what should guide patients and their physicians."

For many nutraceuticals, the most compelling evidence for efficacy remains anecdotal or, at best, based on hints of benefit from small or poorly controlled studies. Still, Weaver says, that doesn't stop several of the researchers at her institute from using nutraceutical supplements themselves. "Anecdotal evidence really shouldn't be very convincing to scientists," she says, "but people remain hopeful." That hope, to a large degree, is what fuels the popularity of dietary supplements. But it's good science that ultimately will determine whether the hope is well placed or not. ■

THOMAS HAYDEN writes about science, medicine and culture from San Francisco.

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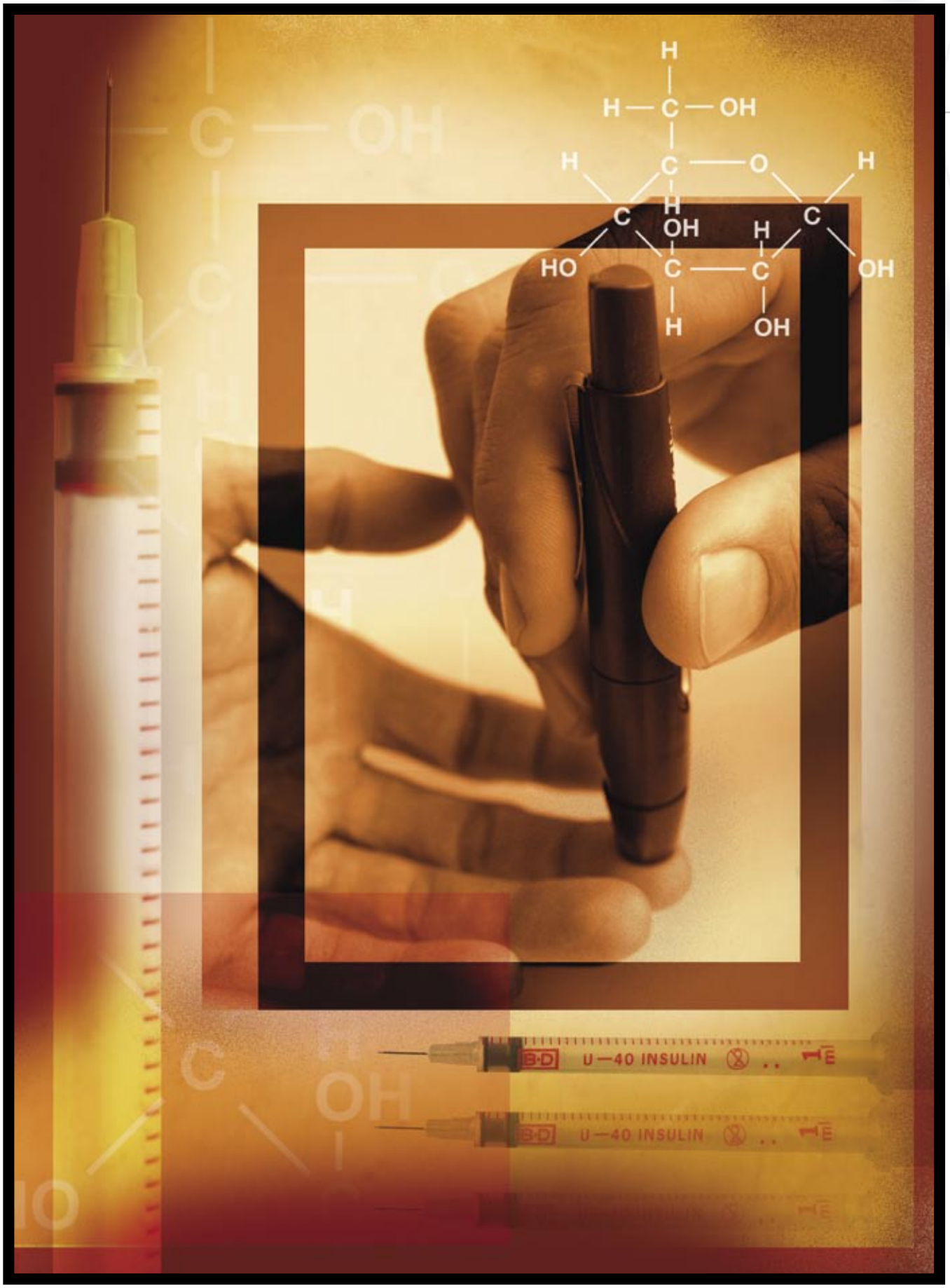

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SPECIAL REPORT

MANAGING Diabetes

More than 171 million people have this increasingly common condition. But lizard spit, new monitors and an array of other drugs and devices can help control diabetes better than ever

By Sara Sklaroff and John Rennie

Diabetes has reached virtually epidemic levels in the modern world. In 2005 the U.S. Centers for Disease Control and Prevention estimated that about 7 percent of the American population (20.9 million people) had diabetes—and 6.2 million of them were unaware of it. More than 1.5 million people over the age of 20 will be diagnosed with it in the U.S. this year. About 21 percent of those older than 60 have the disease.

MIRIAM MASLO *Photo Researchers, Inc. (left);*
GETTY IMAGES *(above)*

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Small wonder, then, given the severe complications associated with diabetes, that it continues to be the sixth leading cause of death in the U.S. And although diabetes was often called a "disease of affluence" in the past, it is now one of the fastest-rising health concerns in developing nations as well: the World Health Organization pegs the global total at more than 171 million cases.

An unfortunate catch-22 of diabetes is that although the right diet and exercise can help with its prevention and management, diabetes itself can complicate both eating and physical activity. Patients may need to pay extra attention to taking meals on a regular schedule and to monitoring how exercise dehydrates them or lowers their blood glucose. Some may fail to comply consistently with prescribed regimens that seem inconvenient or unpleasant, thereby raising their risk of

Complications: The Toll of Diabetes

People with diabetes need to control the abnormally high levels of glucose in their blood because over time that extra sugar can be profoundly harmful to tissues throughout the body. Many patients find that they eventually must treat one or more of the resulting complications, in addition to the underlying diabetes. According to the CDC, some of the most common complications include:

Heart disease, stroke and hypertension. Death rates from heart disease are two to four times higher among adults with diabetes than among their peers without it. The risk of stroke is similarly high. And more than 70 percent of people with diabetes develop a tendency for high blood pressure. Not surprisingly, then, whereas heart disease and stroke account for about 40 percent of all deaths, they kill about 65 percent of the diabetic population. But people with diabetes can reduce their risk for heart disease and stroke by controlling their cholesterol and blood pressure, taking aspirin and not smoking. Though not proved definitively, blood glucose control also probably reduces risk.

Beware of retinal damage and vision loss.

Blindness. Because it can damage the delicate blood vessels in the retina of the eye, diabetes is the leading cause of blindness with onset in adults—between 12,000 and 24,000 new cases every year. Fortunately, blindness can be prevented by controlling blood glucose and blood pressure. Annual eye exams, which can catch problems early, are a must for people with diabetes.

Kidney disease. Diabetes is the number one cause of kidney failure; it was responsible for 44 percent of all cases in 2002. Again, control of glucose and blood pressure, along with annual screening tests, can reduce the risk.

Nervous system disorders. Between 60 and 70 percent of people with diabetes exhibit damage to their nervous systems that ranges from minor to severe. Almost 30 percent of those older than 40 lack at least some sensation in their toes or feet (a condition called peripheral neuropathy). Numbness or pain in the other limbs and sluggish digestion are also common.

Amputation. Partly because diabetic persons may not be aware of injuries or inflammation in numbed feet, they are at higher risk of severe infections that can lead to amputations. More than 60 percent of amputations involving toes, feet and legs (except those resulting from accidents) occur among people with diabetes. Most of those amputations could be prevented with glucose control and more attention to foot care.

Pregnancy problems. When diabetes is not well controlled before conception or in the first trimester, it can lead to spontaneous abortion in as many as 20 percent of pregnancies or to major birth defects. Poor control of diabetes later in the pregnancy can cause the baby to grow unusually large, which is risky to both mother and child.

Other complications. Almost a third of those with diabetes suffer gum disease severe enough to endanger teeth. Diabetic patients are also more likely to die of the flu or pneumonia. And when diabetes is very poorly controlled, people are at risk for developing disruptive biochemical imbalances, such as diabetic ketoacidosis, that can become life-threatening.

The lesson is simple: the more people do to control their diabetes, the better their chances for maintaining good health.

—*J.R.*

VINCENT LAFORET *The New York Times/Redux*

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MORE THAN SIX MILLION AMERICANS HAVE TYPE 2 DIABETES AND DON'T KNOW IT BECAUSE ITS EARLY SYMPTOMS CAN SEEM SO HARMLESS AND VAGUE.

complications. But thanks to leaps in science's understanding of the disease, doctors now wield a diverse and growing arsenal of drugs and management technologies to fight the progression—and even onset—of illness. People with diabetes have more and better options than ever before for enjoying healthy, active, long lives.

BACKGROUND

Diabetes is a disease in which too much of a sugar called glucose accumulates in the blood because of a breakdown in how the body makes or reacts to the hormone insulin. Insulin enables muscle, fat and other types of cells to take up and process glucose. If cells can't burn or store glucose normally and the blood levels rise chronically, damage accumulates throughout the body—in the worst cases leading to blindness, amputation, kidney failure or death.

Most cases fall into one of two categories:

Type 1 diabetes (formerly known as juvenile diabetes) occurs when the body sabotages its own ability to produce insulin. A disorder of the patient's immune system causes it to attack the insulin-making beta cells in the pancreas. Consequently, patients with type 1 diabetes need an artificial source of insulin. Although it is the most common form of diabetes in children, only 5 to 10 percent of all cases of diabetes in the U.S. are of this variety.

Type 2 diabetes, which has become increasingly prevalent during the past few decades, arises from "insulin resistance," which causes cells, for poorly understood reasons, to stop responding properly to the hormone. At first, the pancreas can compensate by producing greater amounts of insulin. But over time, the pancreas reduces its production, making matters worse. Initially this type of diabetes may respond to diet, exercise and weight control, but later medications, and perhaps insulin, may be necessary depending on the severity of the case.

In addition, about 4 percent of all pregnant women develop **gestational diabetes,** a form that usually resolves itself after delivery. Diabetes can also be a rare consequence of certain genetic conditions or chemical exposures.

Regulation of the blood sugar glucose is the cornerstone of diabetes management.

GETTY IMAGES

SYMPTOMS, RISK FACTORS AND DIAGNOSIS

More than six million Americans have type 2 diabetes and don't know it because its early symptoms can seem so harmless and vague:

- Frequent urination
- Extreme thirst and hunger
- Irritability
- Fatigue
- Blurred vision

In contrast, type 1 diabetes comes on more quickly and with more prominent symptoms, such as unexplained rapid weight loss, dehydration or a severe illness called ketoacidosis. Med-

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ical science has still not yet determined precisely why some people develop diabetes and others do not—the genetic and environmental triggers for the disease are surprisingly complex.

For example, type 1 diabetes is not simply genetic in origin, because even the identical twin of someone with diabetes, who shares the same genes, will develop the condition no more than 50 percent of the time. Some as yet unidentified factor in the environment—perhaps a virus—must therefore trigger the immune systems of genetically susceptible people to attack the beta cells in their pancreas. Other environmental factors also seem to be involved: research finds that type 1 diabetes is less common among those who were breast-fed.

For type 2 diabetes, the genetic component is greater: it tends to run more obviously in families, and the identical twin of a person with diabetes will manifest the disease up to 75 percent of the time. Yet it is also very strongly linked to weight gain and insufficient exercise. As the American Diabetes Association (ADA) notes, "[A] family history of type 2 diabetes is one of the strongest risk factors for getting the disease, but it only seems to matter in people living a Western lifestyle." In the U.S., type 2 diabetes is also more common among African-Americans, Latinos, Asians and Native Americans.

Two ways to diagnose diabetes definitively are testing a patient's blood with either a fasting plasma glucose (FPG) test or an oral glucose tolerance test (OGTT). The FPG measures the concentration of glucose in the blood of a person who has been fasting for 12 hours; if it is above 125 milligrams per deciliter, the patient is diabetic. The OGTT measures the subject's blood glucose level both after a fast and two hours after consuming a glucose-rich drink; diabetes is the diagnosis if the latter reading is above 200 milligrams per deciliter. (The ADA favors the FPG because it is less expensive, faster and easier for patients.)

Making smart dietary choices is important for people with diabetes. Foods rich in sugars and carbohydrates should be approached with care.

DANIEL LAI *Getty Images*

PREVENTION AND PREDIABETES

People do not become diabetic overnight. Almost all of those who eventually acquire type 2 diabetes move first through a "prediabetes" state in which their blood glucose levels are elevated but not quite high enough to qualify as diabetes. (Prediabetes is also called impaired glucose tolerance and impaired fasting glucose, depending on the tests used to diagnose it.) Research suggests even those slightly less than diabetic blood glucose levels may do long-term damage to the body, and patients with prediabetes are at a 50 percent higher risk for heart disease and stroke. In a major clinical trial from 2002 called the Diabetes Prevention Program (DPP), roughly 11 percent of those with prediabetes became type 2 diabetics during the three years of the study.

The good news for the estimated 54 million Americans who have prediabetes is that many can prevent their conditions from progressing through moderate exercise and changes to diet. In fact, many of them might even be able to return their blood glucose levels to normal. The DPP found that patients who lowered their body weight by a mere 5 to 10 percent—typically just 10 to 15 pounds—through diet and moderate exercise reduced their risk of developing diabetes by 58 percent. These interventions were even more effective among patients older than 60: their risk fell by 71 percent. And it should go without saying that regular exercise and a healthy diet can help keep people from acquiring prediabetes, too.

MANAGEMENT AND TREATMENT

The main goal in diabetes management is to constantly keep blood glucose levels as normal as possible. Clinical studies have shown that the rate of complications from the disease drops

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markedly when this standard is maintained over long periods.

But doing so is not just a matter of swallowing a pill or taking a shot. People with the condition need to steadily monitor their blood glucose levels or to anticipate changes in them and respond appropriately. To state the obvious: a sound program of diabetes management and treatment needs to be developed with a qualified health care team.

Monitoring blood glucose. All people with diabetes should periodically have a hemoglobin A1c test, which indicates the patient's average blood glucose concentration over the preceding three months. This measurement is often the best way to see how well a treatment is going overall. Depending on his or her situation, a patient might also be monitoring daily blood glucose levels with a home blood tester. Typically this test involves pricking a finger (or palm or arm) with a trigger-style lancet, applying the drop of blood to a test strip and inserting it into a digital reader.

In a major technical advance, three companies have recently introduced continuous glucose-monitoring systems, which sample blood glucose levels many times over the course of the day with small radio-equipped sensors embedded under the skin [see "Monitoring: An End to Pricked Fingers," below, and "Docs on Call,"

Monitoring: An End to Pricked Fingers

Finger-stick monitors have long been the only way for people with diabetes to determine their glucose levels on a day-to-day basis. Anywhere from twice a week to several times a day, patients jab their fingers with small lancet needles to draw drops of blood that can then be slipped into a monitor to measure the concentration of the glucose in their blood. Aside from the pain and inconvenience, such occasional blood sampling is less than ideal for maintaining healthy glucose levels.

But the era of lancet pricks may be coming to an end. In the past few years, three companies—Medtronic Diabetes, DexCom and Abbott Diabetes Care—have introduced the first personal continuous glucose-monitoring devices, a new technology that relies on a sensor implanted underneath the skin to send information on glucose levels via a radio transmitter to a pager-size monitoring device. These gadgets are not yet a permanent solution for glucose monitoring: the FDA has only approved sensors that measure continuously for three to seven days, when the sensors have to be replaced.

Medtronic's Real-Time continuous glucose monitor.

COURTESY OF MEDTRONIC DIABETES

Still, continuous glucose monitors are allowing patients to access a previously unimaginable amount of information about their bodies. The tiny rechargeable, waterproof sensor on Medtronic's Real-Time continuous glucose monitor, for example, sends measurements to the monitor every minute. The device then displays an average of the last five minutes' worth of data. In total, it generates some 288 readings every day—almost 100 times as many as patients using a traditional monitor. The device provides readings of daily glucose highs and lows, and it also integrates trends in the data, which can then be downloaded onto a computer. This minute-by-minute catalogue allows users to see exactly how certain foods and activities affect their bodies. Medtronic also offers a version of the device that interacts with its insulin pump, which displays information from the sensor, allowing users to adjust insulin levels more conveniently.

While these devices offer a glimpse into an exciting future—eventually the monitors may be able to automatically adjust insulin pump doses, operating as a kind of mechanical pancreas—a few major obstacles remain in the short term. For one thing, continuous glucose monitors are not automatically covered by insurance unless a patient shows a specific need. Subcutaneous sensors also have their drawbacks. Because they are implanted in tissue underneath the skin and not in the bloodstream itself, they don't always register the exact glucose levels in the body. Subcutaneous glucose levels tend to lag those in the bloodstream, making calibration a problem. To avoid this discrepancy, Abbott's device, the Navigator, doesn't allow itself to be calibrated if glucose levels are rising. Abbott's monitor is the only one of the three companies' devices that has not yet received FDA approval, although it is expected later this year. —*Justin Ewers*

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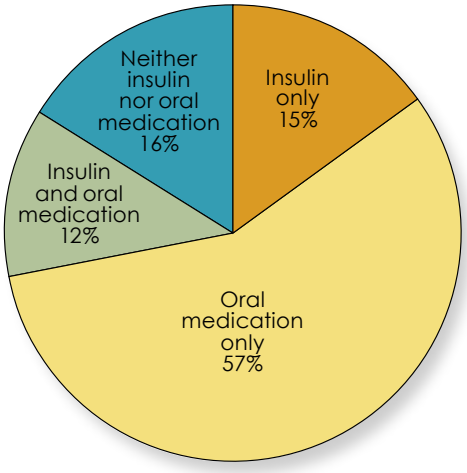
SUCH UNITS COULD EVENTUALLY BE PART OF A "MECHANICAL PANCREAS" THAT WOULD BOTH SENSE GLUCOSE IN THE BLOOD AND ADMINISTER INSULIN ACCORDINGLY.

How U.S. Adults with Diabetes Treat It



SOURCE: 2001–2003 National Health Interview Survey

below]. The systems can be programmed to sound an alarm if blood glucose goes too high or too low. Such units could eventually help revolutionize the treatment of type 1 diabetes in particular: linked to pumps for delivering insulin, they could be part of a "mechanical pancreas" that would both sense glucose in the blood and administer insulin accordingly.

Insulin. Until the 1920s, when type 1 was still the dominant form, a diagnosis of diabetes was virtually a death sentence. That all changed with the identification and isolation of insulin, which made it possible to treat the condition for the first time.

But making use of insulin began as a messy process. Running animal pancreases through a meat grinder to obtain insulin yielded a murky liquid with difficult-to-predict efficacy levels, which sometimes provoked allergic reactions.

Docs on **Call**

As diabetes treatment goes high-tech, diabetics are exposed to ever growing amounts of information about the state of their bodies—and many of those people are starting to wonder what they're going to do with it all. Devices such as continuous glucose-monitoring systems offer one way of analyzing this growing stream of data, but other options exist as well. InterMed Health Technologies in Cambridge, Mass., for example, offers the Patient Data Handler (PDH), a device that wirelessly interacts with a regular glucose meter, automatically recording the readings after each blood test. Piggybacking on traditional diabetes technology, the PDH sends the patient's health information via modem or broadband connection to a central server every night, where InterMed's software analyzes it and produces a personalized feedback report, which is then e-mailed to the patient and care provider. Because it's wireless, this data transfer requires no action by the user. InterMed, which offers similar systems for people with asthma and heart problems, is currently working on enrolling patients in the system through HMOs.

InterMed's Patient Data Handler.

COURTESY OF INTERMED HEALTH TECHNOLOGIES, INC.

Those who prefer measuring their glucose on the go can choose other alternatives. HealthPia America, a New Jersey–based biotech company, offers a handy glucose-measuring device called the GlucoPack that can be fitted onto a regular cell phone. The system works just like a standard glucose meter: patients test their blood using a traditional lancet, then use a special strip stored in the cell phone to analyze it. The information is downloaded to the phone, where it can be text-messaged to a caregiver. HealthPia's system was first tested in South Korea but received FDA approval in 2006. —*Justin Ewers*

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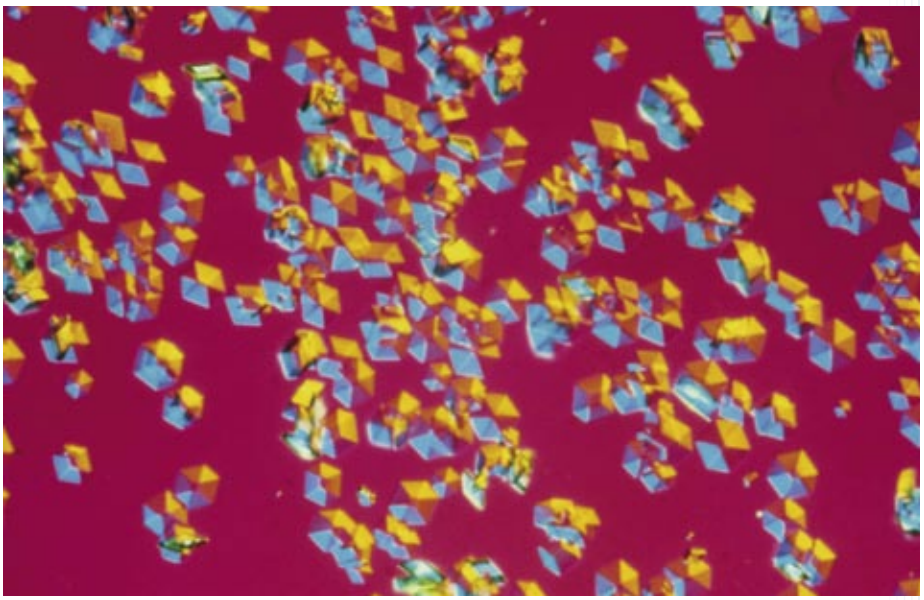
Because digestive enzymes destroy the insulin molecule, it cannot be taken orally: insulin had to be injected under the skin with a syringe. Moreover, delivering insulin in ways that most closely mimicked the body's natural hormone action was a challenge.

Over the decades, however, every aspect of insulin therapy has improved:

Better insulins. Thanks to recombinant DNA technology, since 1982 the biotechnology industry has been able to mass-produce human insulin proteins by growing them in bacteria. Such insulin behaves more like the body's own than animal proteins can and is less allergenic. All insulin sold in the U.S. is now of this human type.

Normally a pancreas releases small amounts of insulin into the circulation constantly, with bigger infusions at mealtimes. Most people who take insulin therefore use two types: a long-acting "basal" insulin administered once or twice a day and a rapid-acting "bolus" insulin before meals. In recent years, pharmaceutical companies have further reformulated the human insulins to create faster-, slower- and intermediate-working versions, with different durations of



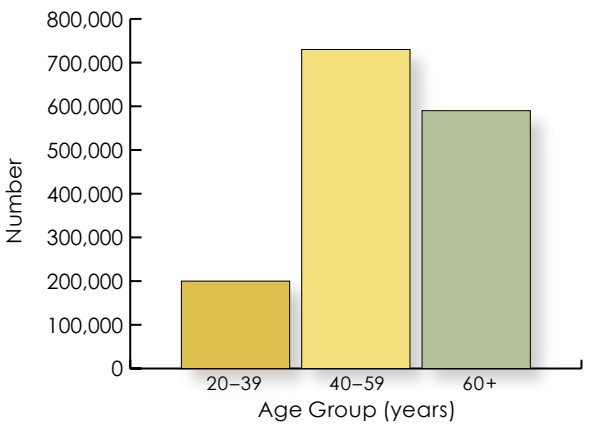
ALFRED PASIEKA *Photo Researchers, Inc.*

Crystals of insulin as seen through a microscope.

Incidence of Diabetes in the U.S.

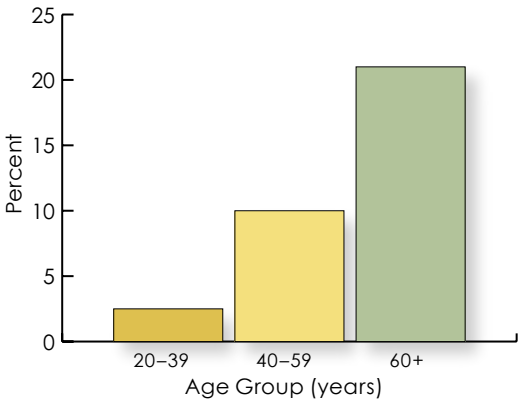
1.5 million new cases of diabetes were diagnosed in people aged 20 years or older in 2005

Estimated number of new diagnosed cases



SOURCE: 2001–2003 National Health Interview Survey. Estimates are projected to 2005.

Estimated total prevalence



SOURCE: 1999–2002 National Health and Nutrition Examination Survey. Estimates of total prevalence (both diagnosed and undiagnosed) are projected to 2005.

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Medications: Edging Closer to a Cure

Diabetes drugs help to manage the body's constantly fluctuating levels of blood glucose. But a healthy biochemical balance of the hormones involved in that process—insulin, incretins and more—is painfully delicate. Diabetes medications have consequently often had side effects that were unpleasant (such as weight gain) and, in a few cases, even dangerous. Witness Avandia, a popular drug available since 1999 that lowers blood glucose by making cells more receptive to insulin—but that also, according to a report published in the *New England Journal of Medicine* in May, increases the risk of heart attack.

Which is why the next generation of drugs has doctors so hopeful. By targeting different hormones that help the body manage its own insulin levels—and by reducing side effects such as weight gain—three drugs recently approved by the FDA avoid most of the major problems associated with past diabetes treatments. The drugs are not a replacement for insulin, but they do more than any drug in the past to assist the body in making its own. And although they may represent only another small step toward a "cure" for diabetes, they are beginning to provide patients with levels of control never before seen over their own hormones.

Byetta (exenatide), for example, made by Eli Lilly and Amylin Pharmaceuticals and approved by the FDA in 2005, mimics a hormone, incretin, that stimulates the pancreas to produce insulin in response to elevated blood glucose—something healthy pancreases do naturally. The injectable drug was inspired by the digestive system of the Gila monster, which needs to eat only three or four times a year; a chemical compound in the lizard's saliva called exendin-4 seems to jumpstart its pancreas after its multimonth fasts. Exenatide, which is derived from that same compound, increases the insulin produced in response to meals and slows the absorption of carbohydrates in humans. Byetta therefore not only helps patients with type 2 diabetes control their glucose levels, but it also reduces appetite, leading to weight loss.

Byetta

Another drug made by Amylin Pharmaceuticals and approved by the FDA in 2005, Symlin (pramlintide), has a similar effect. Symlin, which is for both type 1 and 2 diabetes, simulates a different hormone, amylin, which is secreted by the pancreas along with insulin after meals. Often referred to as a satiety hormone, amylin makes the body feel full by slowing the rate at which food passes from the stomach to the intestines. On average, people taking injections of Symlin ate significantly fewer calories per day, according to a study sponsored by the company. Losing weight can itself help improve diabetes. For both Byetta and Symlin, however, nausea is a significant side effect, so neither is a perfect therapy.

Symlin

Then there is Januvia (sitagliptin phosphate) for type 2 diabetics, produced by Merck and approved in October 2006. An oral tablet taken once daily, Januvia is the first in a new line of pharmaceuticals that raise incretin levels in the body by inhibiting the production of DPP-4, an enzyme that naturally destroys incretins. Blocking DPP-4 also signals the liver to release less glucose into the blood, thereby lowering the body's need to produce insulin. The drug also reduces weight gain.

Januvia

A few potential complications are associated with all three new drugs. Delaying the emptying of the stomach, for example, can make timing insulin injections more difficult—and will certainly require more individualized dosing regimens. It also isn't clear what Januvia's effects on breaking down hormones, in particular, will have on long-term toxicity levels in the body. Some doctors still hesitate to prescribe it for this reason.

—Justin Ewers

ELI LILLY AND COMPANY (*Byetta*); MERCK & CO., INC. (*Januvia*); COURTESY OF AMYLIN PHARMACEUTICALS, INC. (*Symlin*)

action, all in an attempt to re-create what the human body does.

Nicer needles. Insulin-dependent patients used to depend on large-bore needles that were relatively expensive and quickly went dull. Today's syringes have extremely small gauge needles that can be surprisingly painless. Some insulins are packaged inside pen-shaped injectors, eliminating the need for drawing fluid out of a vial with a syringe. The pen contains many doses of insulin; new disposable needles are attached for each dosage. It makes injecting in public far more discreet.

Alternatives to injection. To most people, needle sticks are fundamentally unpleasant. So researchers have been trying to figure out easier

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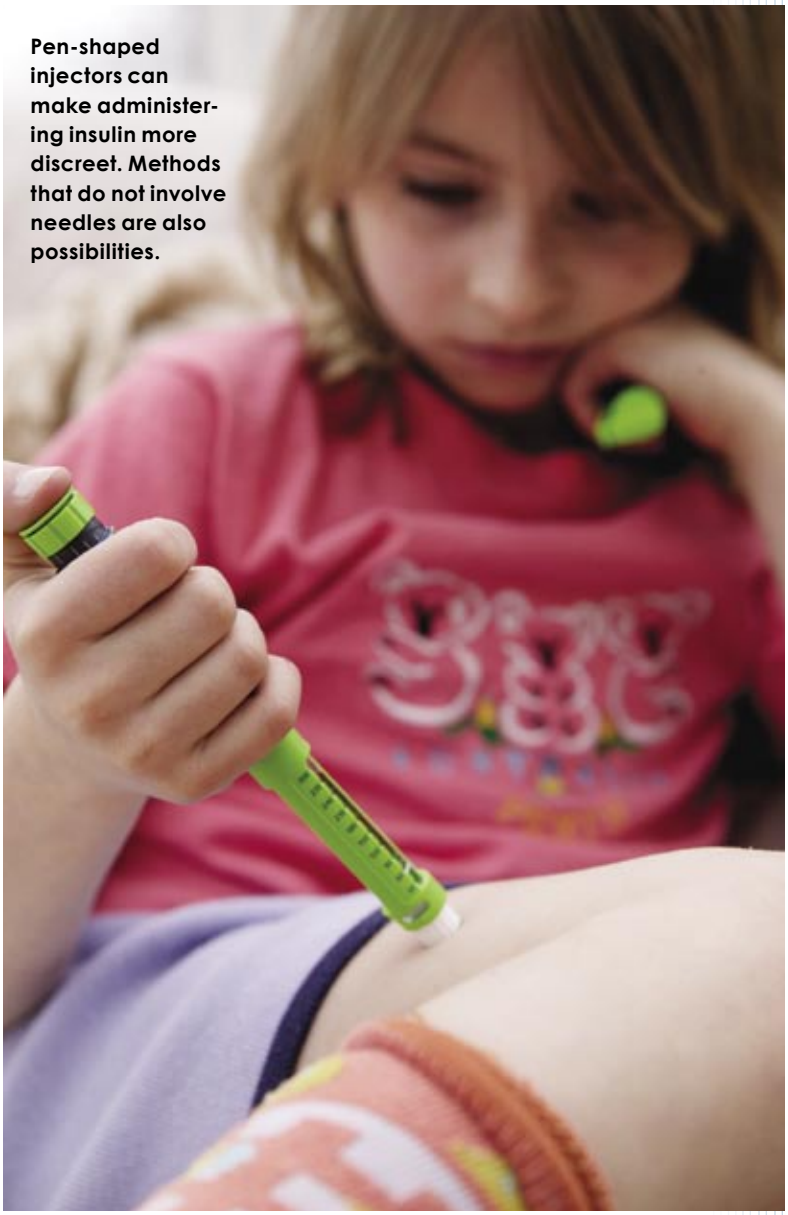
TO MOST PEOPLE, NEEDLE STICKS ARE FUNDAMENTALLY UNPLEASANT. SO RESEARCHERS HAVE BEEN TRYING TO FIGURE OUT EASIER WAYS TO GET INSULIN INTO THE SYSTEM.

ways to get insulin into the system. One step in that direction is the insulin pump, a pagerlike device that is worn continually and can be programmed to deliver both basal and bolus infusions through a catheter inserted under the skin. For some patients, this system is more discreet and effective than syringe injections can be. Still, pump supplies are more expensive, and care must be taken during exercise that the pump is not dislodged or damaged.

Another alternative is inhalable insulin. Pfizer introduced a version (Exubera) in 2006, but withdrew it from the market last fall, perhaps because of a somewhat unwieldy apparatus (the "insulin bong," as some have dubbed it), the additional training required to use the device and lingering questions about long-term pulmonary effects. Other delivery methods are still under investigation, including a nasal spray, a self-contained implantable pump and a transdermal patch that uses electric current to move insulin across the skin barrier.

The ideal would be an effective oral version of insulin that could avoid destruction in the digestive tract. A number of companies are working on developing oral insulins, and Generex Biotechnology has an oral insulin spray approved for sale in Ecuador; however, similar products may be years away from proving safe and effective enough to satisfy the U.S. Food and Drug Administration [see also "A Mishandled Delivery for Insulin," on next page].



Pen-shaped injectors can make administering insulin more discreet. Methods that do not involve needles are also possibilities.

MICHAEL DONNE *SPL/Photo Researchers, Inc.*

OTHER MEDICATIONS

Most people with diabetes do not need to take insulin, because their bodies still make some. Instead they take medications that can help them produce more insulin or use it better. Until recently, these oral meds fell into five categories: alpha glucosidase inhibitors (Precose, Glycet), metformin, meglitinides (Starlix, Prandin), sulfonylureas, and thiazolidinediones (Avandia and Actos, which have been in the headlines because of persistent concerns over their cardiovascular effects). A newer class is the DPP-4 inhibitors (Januvia is the only drug of this type available so far), which help to maintain levels of GLP-1, an intestinal hormone that promotes insulin production.

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A Mishandled Delivery for Insulin

For decades, there was only one way to get insulin into the body: injection under the skin. Insulin pens and pumps offered some measure of discretion and flexibility, but people uncomfortable with needles and catheters have been, in a word, stuck.

Not for long. Scientists are developing a range of new ways to deliver insulin to the body. Some of these ideas are still in the prototype stage, including a patch that administers insulin through the skin just as a nicotine patch administers nicotine. Encapsulation Systems in Havertown, Pa., for example, has successfully conducted human trials on its first insulin patch, but the device is still not yet FDA-approved.

Several other small companies, including Bentley Pharmaceuticals in Exeter, N.H., are conducting clinical trials on insulin nasal sprays as well. Whereas sprays and patches are still years away from FDA approval, there have been some very real steps away from needles. Exubera, for example, an inhaled insulin made by Pfizer that was approved by the FDA in 2006, was the first new insulin-delivery option on the market since insulin was discovered in the 1920s. But the others are on their way: a handful of major pharmaceutical companies have reached the last phase of clinical trials.

Some people with diabetes may wonder why the "insulin bong," the nickname given to the Exubera inhaler because of its distinctive shape, needed to look quite so much like drug paraphernalia, but the more enduring question was whether it worked. Inhaling insulin certainly has some advantages: for one, it allows the body to reach peak insulin levels much more quickly than injections can. On average, Exubera users attained peak levels in 49 minutes, compared with 105 minutes for regular insulin.

Exubera insulin inhaler.

But inhalers do have their drawbacks. Some concerns persist about inhaled insulin's effect on the lungs. In clinical trials, some patients experienced reduced lung function, which Pfizer, on further study, found to be medically insignificant. Respiratory infections can also make absorption difficult—which could make a common cold potentially dangerous for people who rely on inhaled insulin. Unlike asthma, which is commonly treated with an inhaler, diabetes requires very precise insulin doses; despite Pfizer's insistence, some doctors weren't convinced inhalers would be able to offer the same degree of exactness as an injection. Exubera also didn't necessarily mean the end of needles: because it was only available as a rapid-acting insulin for mealtimes, patients still had to inject long-acting insulin as part of their daily routine. *—Justin Ewers*

Excitement also surrounds two other new classes of drugs: incretin mimetic agents (Byetta, derived from the saliva of the Gila monster, is the only one currently on the market) and amylin analogues (Symlin is the first to be approved). Incretins are hormones that the digestive tract releases in response to carbohydrates and fats and that tell the pancreas to secrete extra insulin. Amylin is another hormone produced by the pancreas, and it helps to depress blood glucose.

Like insulin, both incretin mimetics and amylin analogues must be injected. They both have a beneficial side effect, however: they slow the emptying of the stomach. As a result, people feel full sooner, eat less and often lose weight on these drugs, which in itself can improve their diabetes [see also "Medications: Edging Closer to a Cure," on page 54].

EXTREME TECHNIQUES

For some patients, dramatic measures may be called for. Gastric bypass or reduction surgery, which shrinks the space in the stomach for food, can sometimes almost eliminate type 2 diabetes in morbidly obese patients (the surgery carries its own risks, however). For a few people with type 1 diabetes, one option might be a pancreas transplant, to replace the insulin-making beta cells they have lost. But this surgery, too, can be hazardous, and few pancreases are available for transplantation. Moreover, to prevent the patient's immune system from rejecting the new pancreas, he or she would need to take immunosuppressive drugs for life, which can also be dangerous.

A potentially safer (and less expensive) choice could someday be the experimental procedure of

SCOTT CAMAZINE *Phototake*

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TO PREVENT THE PATIENT'S IMMUNE SYSTEM FROM REJECTING THE NEW PANCREAS, HE OR SHE WOULD NEED TO TAKE IMMUNOSUPPRESSIVE DRUGS FOR LIFE.

An insulin pump worn on the belt like a pager can supply the hormone at an adjustable rate through a tube.

PHANIE *Photo Researchers, Inc.*

transplanting just the pancreatic islet clusters that contain the beta cells. Such implants would involve less trauma than replacing an entire pancreas, and it might be possible to encase the grafted cells in packaging that would protect them from the immune system. Researchers are also working on using highly versatile stem cells, which can give rise to new tissues, to replace lost beta cells. The early results are guardedly positive, but it will be years, if ever, before such a technique becomes widely available. ■

Contributors to this special report include Sara Sklaroff, a science writer and editorial director for the American Diabetes Association magazine Diabetes Forecast; *Justin Ewers, a science writer based in San Francisco; and John Rennie, editor in chief of* Scientific American.

More to Explore

- **www.SciAm.com/Body** features a full array of content on the subject of diabetes, including a version of this article hyperlinked to other resources online.
- **American Diabetes Association** is the leading nonprofit health organization for diabetes research, information and advocacy. A full list of its diabetes-awareness events in your area can be found on **www.diabetes.org**. Also available is highly readable background information about prevention and treatment.
- **National Diabetes Information Clearinghouse** (**http://diabetes.niddk.nih.gov**), as its name suggests, is a repository of links to diverse, helpful resources maintained by the National Institute of Diabetes and Digestive and Kidney Diseases.

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Is There *Really* an Autism Epidemic?

A CLOSER LOOK AT THE STATISTICS SUGGESTS SOMETHING MORE THAN A SIMPLE RISE IN INCIDENCE

By Scott O. Lilienfeld and Hal Arkowitz

If the statistic "one in 166" has a familiar ring, perhaps that's because you recently heard it on a television commercial or read it in a magazine. According to widely publicized estimates, one in 166 is now the proportion of children who suffer from autism. This proportion is astonishingly high compared with the figure of one in 2,500 that autism researchers had accepted for decades. Across a mere 10-year period—1993 to 2003—statistics from the U.S. Department of Education revealed a 657 percent increase in the nationwide rate of autism.

Not surprisingly, these bewildering increases have led many researchers and educators to refer to an "autism epidemic." Representative Dan Burton of Indiana also declared in 2001 that "we have an epidemic on our hands." But what's really going on?

Before we explore this question, a bit of background is in order. Autism is a severe disorder that first appears in infancy. Individuals with autism are characterized by problems with language, social bonding and imagination. All suffer from serious communication deficits, and some are mute. They do not establish close relationships with others, preferring to remain in their own mental worlds.

CAROL AND MIKE WERNER *Phototake*

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RECENTLY PUBLISHED RESEARCH HAS NOT BEEN KIND TO THE MUCH BALLYHOOED VACCINE-AUTISM LINK.

They engage in highly stereotyped and repetitive activities, exhibiting a marked aversion to change. About two thirds of autistic individuals are mentally retarded. For reasons that are unknown, most are male.

The causes of autism remain enigmatic, although studies of twins suggest that genetic factors play a prominent role. Still, genetic influences alone cannot account for such a rapid and astronomical rise in a disorder's prevalence over a matter of just a few years. As a consequence, investigators have turned to environmental factors for potential explanations. The causal agents proposed include antibiotics, viruses, allergies, enhanced opportunities for parents with mild autistic traits to meet and mate, and, in one recent study conducted by Cornell University researchers, elevated rates of television viewing in infants. Few of these explanations have been investigated systematically, and all remain speculative.

ARE VACCINES THE PROBLEM?

Yet one environmental culprit has received the lion's share of attention: vaccines. At first blush, vaccines would seem to make a plausible candidate for the source of the epidemic. The debilitating symptoms of autism typically become apparent shortly after age two, not long after infants have received vaccinations for a host of diseases. Indeed, many parents claim that their children developed autism shortly after receiving inoculations, either following a vaccine series for mumps, measles and rubella (German measles)—the so-called MMR vaccine—or following vaccines containing thimerosal, a preservative that contains mercury.

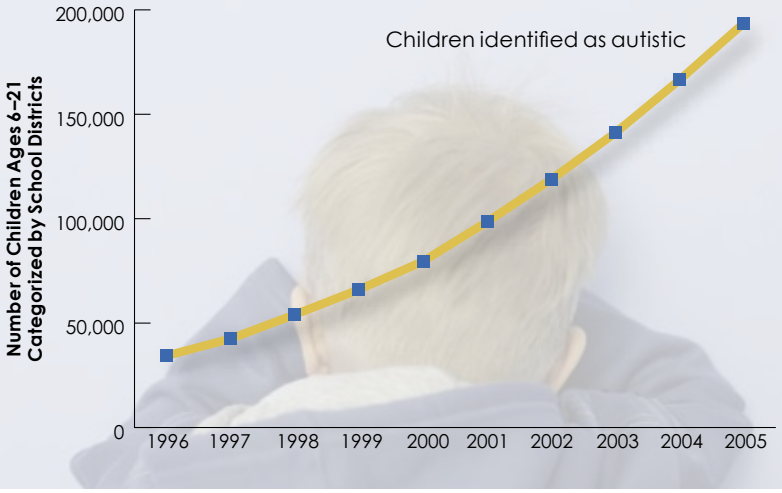
Much of the hype surrounding a link between vaccines and autism was fueled by a widely covered investigation of 12 children published in 1998 by British gastroenterologist Andrew Wakefield and his colleagues. The study revealed that symptoms of autism emerged shortly after the children received the MMR vaccine. (Ten of the 13 authors have since published a retraction of the article's conclusions.) Public interest in the vaccine-autism link was further stoked by the provocatively entitled book *Evidence of Harm* (St. Martin's Press, 2005), written by investigative journalist David Kirby, which was featured in an extended segment on NBC's *Meet the Press*.

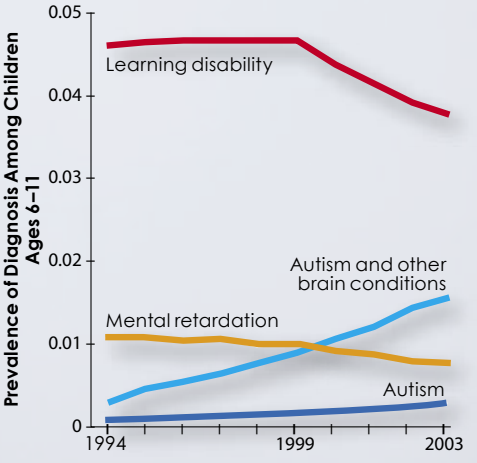
Yet recently published research has not been kind to this much ballyhooed link. The results of several large American, European and Japanese studies demonstrate that although the rate of MMR vaccinations has remained constant or declined, the rate of autism diagnoses has soared. In addition, after the Danish government stopped administering thimerosal-bearing vaccines, the rates of autism continued to rise. These studies and others summarized by the Institute of Medi-

More Autism … or Different Labeling?

Soaring numbers of children reported as autistic by school districts are often cited as proof that the incidence of the condition is rising (*left*). But changes in diagnostic criteria could also account for that pattern. One study found that as autism seemingly increased, the prevalence of learning disabilities and mental retardation dropped—which suggests that in some cases, one diagnosis substituted for another (*right*).

—The Editors





SOURCES: INDIVIDUALS WITH DISABILITIES EDUCATION ACT DATA WEB SITE (WWW.IDEADATA.ORG) (*left graph*); "THE CONTRIBUTION OF DIAGNOSTIC SUBSTITUTION TO THE GROWING ADMINISTRATIVE PREVALENCE OF AUTISM IN US SPECIAL EDUCATION," BY PAUL T. SHATTUCK, IN *PEDIATRICS*, VOL. 117, NO. 4; APRIL 2006 (*right graph*); GETTY IMAGES (*boy*)

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cine suggest there is little evidence that vaccines cause autism. It is possible that vaccines trigger autism in a small subset of children, but if so that subset has yet to be identified.

CHANGING CRITERIA

Making matters more confusing, ample reason exists to question the very existence of the autism epidemic. Vaccines may be what scientists call an "explanation in search of a phenomenon." As University of Wisconsin–Madison psychologists Morton Ann Gernsbacher and H. Hill Goldsmith and University of Montreal researcher Michelle Dawson noted in a 2005 review, there is an often overlooked alternative explanation for the epidemic: changes in diagnostic practices. Over time the criteria for a diagnosis of autism have loosened, resulting in the labeling of substantially more mildly afflicted individuals as autistic.

Indeed, the 1980 version of the American Psychiatric Association's diagnostic manual (*DSM-III*) required individuals to meet six of six criteria for an autism diagnosis. In contrast, the 1994 version (*DSM-IV*), which is currently in use, requires individuals to meet any eight of 16 criteria. Moreover, whereas *DSM-III* contained only two diagnoses relevant to autism, *DSM-IV* contains five such diagnoses, including Asperger's syndrome, which most researchers regard as a high-functioning variant of autism.

Legal changes may also be playing a significant role. As Gernsbacher and her colleagues have noted, an amended version of the Individuals with Disabilities Education Act (IDEA), passed by Congress in 1991, requires school districts to provide precise counts of children with disabilities. IDEA has resulted in sharp surges in the reported numbers of children with autism. Nevertheless, these numbers are not based on careful diagnoses of autism or on representative samples of the population. As a consequence, researchers who rely on "administrative-based estimates," which come from government data submitted by schools, will arrive at misleading conclusions about autism's prevalence.

They must instead rely on "population-based estimates," which are developed from statistically reliable and representative surveys of autism's occurrence in the general population. Further contributing to the reported increase may be the "Rain Man effect," the public's increased familiarity with autism following the 1988 Academy Award–winning film starring Dustin Hoffman and Tom Cruise.

More to Explore

- **Immunization Safety Review: Vaccines and Autism.** Immunization Safety Review Committee. Board of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, 2004. This comprehensive review of the evidence found no reason to believe that the MMR vaccine causes autism.
- **Three Reasons Not to Believe in an Autism Epidemic.** M. A. Gernsbacher, M. Dawson and H. H. Goldsmith in *Current Directions in Psychological Science,* Vol. 14, pages 55–58; 2005. The authors argue that misunderstanding of diagnostic criteria and statistics relating to autism explains why the public's perception of the problem is at odds with the facts. Available at **www.autcom.org/pdf/epidemic.pdf**

SWAPPED DIAGNOSES

Two recent studies buttress assertions that the autism epidemic may be more illusory than real. First, in 2005 psychiatrist Suniti Chakrabarti of the Child Development Center in Stafford, England, and psychiatrist Eric Fombonne of McGill University conducted an investigation that used rigorous population-based estimates to track the prevalence of autism diagnoses from 1992 to 1998 in a sample of more than 10,000 children in the same area of England. They found no support for a change in prevalence, suggesting that when researchers maintain the same criteria for autism, the rates of diagnosis do not change over time.

Second, a 2006 article by University of Wisconsin–Madison psychologist Paul Shattuck cited "diagnostic substitution": as the rates of the autism diagnosis increased from 1994 to 2003, the rates of diagnoses of mental retardation and learning disabilities decreased. It is possible that the overall "pool" of children with autismlike features has remained constant but that the specific diagnoses within this pool have switched.

It is still too early to exclude the possibility that autism's prevalence is growing, but it is unlikely that it is growing as swiftly as many have suggested. As the late Eastern Michigan University sociologist Marcello Truzzi once said, extraordinary claims require extraordinary proof. The claim of an enormous epidemic of autism diagnoses is indeed extraordinary. Yet the evidence for this claim leaves much to be desired. ■

SCOTT O. LILIENFELD and **HAL ARKOWITZ** are columnists for *Scientific American Mind.* Lilienfeld is a psychology professor at Emory University, and Arkowitz is a psychology professor at the University of Arizona.

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SILK SCAFFOLDS, GRAFTS FROM PIGS AND GREEN TEA EXTRACTS MIGHT SOMEDAY HELP KEEP INJURED AND VULNERABLE JOINTS ACTIVE

By Karen Hopkin

Saving Troubled Knees

The patient was clearly in pain. Doctors were not sure how Johnny, a middle-aged male, had hurt his left knee, but they wanted to assess the damage. So they reached for an arthroscope, a video camera on a flexible, pencil-thin tube, and inserted it into the joint through a small incision.

Although arthroscopic surgery is fairly routine for diagnosing and treating knee injuries, Johnny's procedure was anything but. That's because Johnny is a monkey: an 11-year-old mandrill at the Pittsburgh Zoo. "There's no precedent," says Freddie Fu of the University of Pittsburgh School of Medicine, the surgeon who performed the operation in June. "I think this is maybe the first time anyone has ever 'scoped a monkey knee."

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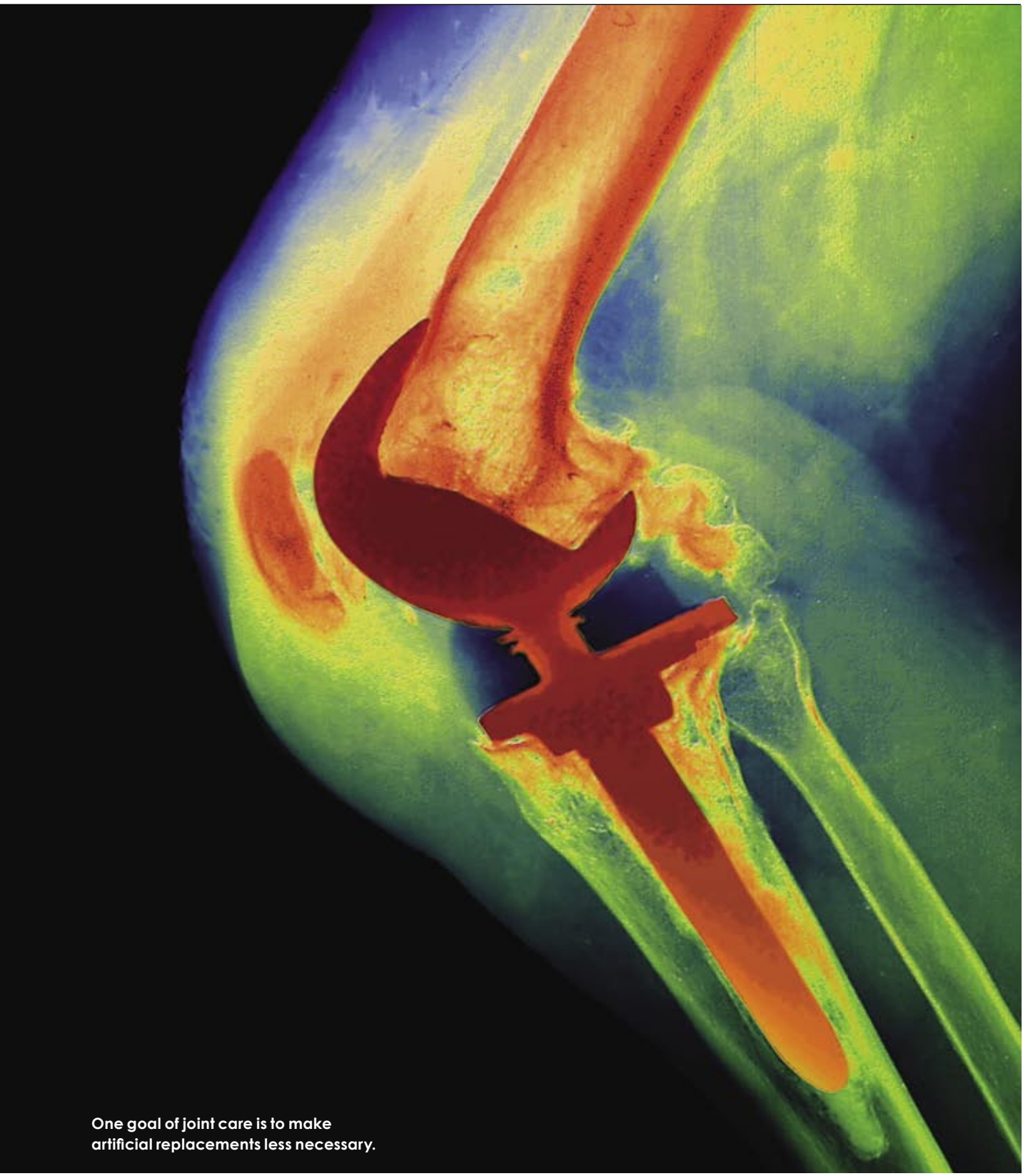

One goal of joint care is to make artificial replacements less necessary.

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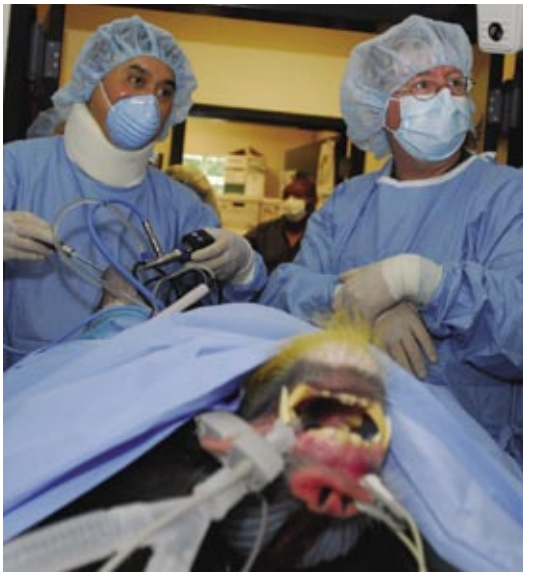
PHYSICIANS RECONSTRUCT ABOUT **200,000 ACLs** EVERY YEAR IN THE U.S. ALONE.

What Fu found is that Johnny had partially torn his anterior cruciate ligament (ACL), a band of tissue that stabilizes the knee, particularly as it rotates. "A torn ACL is one of the most common major injuries in the sports world," says Fu, who guesses that he has mended some 5,000 ligaments during his 30 years in the orthopedic business. Such knee injuries are not limited to professional athletes, however: they can befall just about anyone who is physically active, including weekend warriors, high school students and—as Fu discovered—middle-aged mandrills. Sources in the orthopedic industry estimate that physicians reconstruct about 200,000 ACLs every year in the U.S. alone; worldwide the number of reconstructions may reach up to half a million.

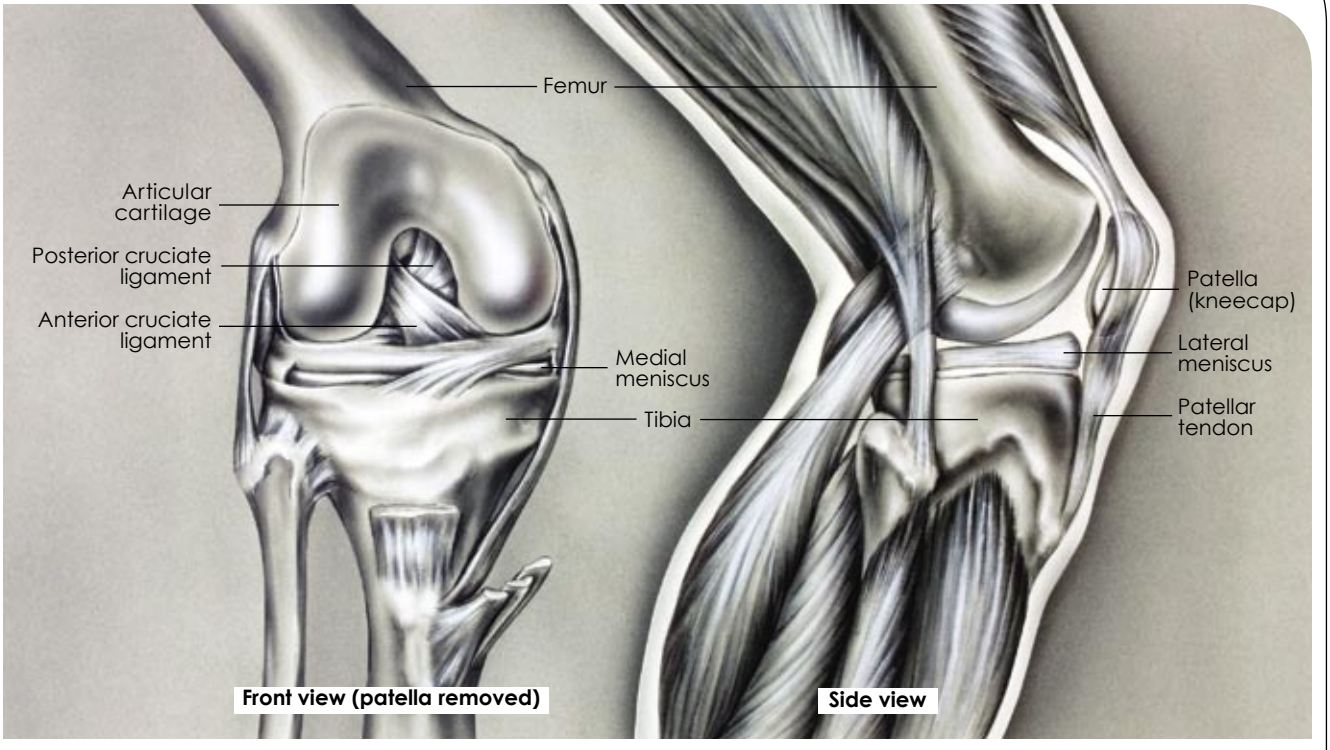
But the problem doesn't end there. Tearing an ACL—even if the ligament subsequently gets repaired—can set the stage for osteoarthritis, a condition in which the entire joint begins to deteriorate. According to one Norwegian study, "100 percent of women who tear their ACL are going to have arthritis in that knee by 20 years out," says Tim Hewett, director of the Sports Medicine Biodynamics Center at Cincinnati Children's Hospital.

Even without an obvious injury to trigger it, osteoarthritis of the knee affects 6 percent of adults older than 30 and 12.5 percent of those older than 60. "This is an extremely common disease," says David Felson, a rheumatologist who specializes in osteoarthritis at the Boston



Johnny the mandrill, shown here under sedation, underwent knee-repair surgery for an anterior cruciate ligament (ACL) injury.

Inside the Right Knee



PAUL A. SELVEGGIO (*top*); JUDITH GLICK *Phototake* (*bottom*)

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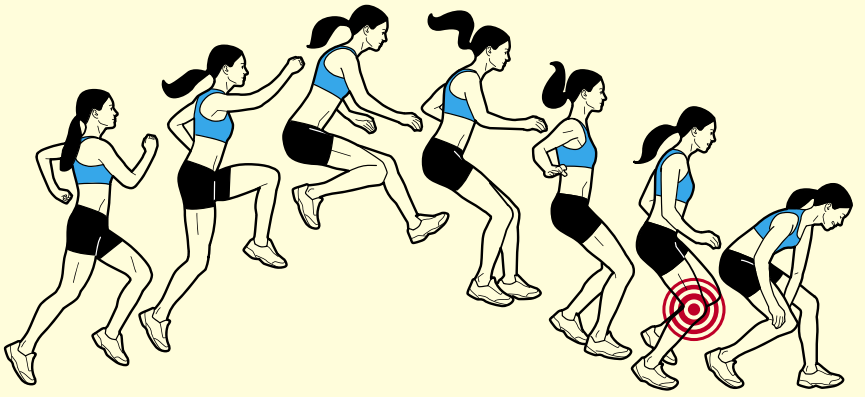
An Ounce of Squatting . . .

Female athletes are between two and six times more likely to tear their anterior cruciate ligaments (ACLs) than their male counterparts are—a problem that provokes Tim Hewett of the University of Cincinnati School of Medicine. "I grew up in a house with six sisters—and most of them were better athletes than me," he says. One tore her ACL playing ball, and Hewett now has a $3-million grant from the National Institutes of Health essentially to figure out why.

Hewett's hunch is that females' additional risk of injury has something to do with neuromuscular control and how athletes manage their body's movements through space. In a paper published last year, Hewett and his colleagues reported that training female athletes to use their musculature to better absorb force and properly position their knees, feet and trunks lowered their risk of knee and ACL injuries by 30 to 80 percent. "If females are five times more likely to sustain an injury, an 80 percent decrease in risk is going to bring them down to where the males are," Hewett says. "What that says to me is that a big player in this difference is neuromuscular control."

HEWETT'S HUNCH IS THAT FEMALES' **ADDITIONAL RISK OF INJURY** HAS SOMETHING TO DO WITH NEUROMUSCULAR CONTROL AND HOW ATHLETES MANAGE THEIR MOVEMENTS.



Motion studies suggest that the ways in which female athletes use their muscles—for example, when landing from a jump—may predispose them to ACL injuries.

Hewett has been working on the problem for 15 years, first identifying neuromuscular quirks that are significantly more common in young female athletes than in males—especially in females who go on to get injured. His experimental subjects: "every soccer and basketball player in the sixth through 12th grades in the entire [Boone County, Kentucky] school system," he says. "We bring 'em in by the busload." Hewett and his co-investigators attach 37 reflective markers to each athlete's body and then watch them play. By recording the kids' movements as they run and jump, zigzag and land—all on a floor covered with force plates—Hewett and his colleagues can generate computer models of their every motion and measure the amount of force on their joints.

Reviewing that data, Hewett has learned several things. First, boys flex their legs and use their muscles—their hamstrings, in particular—to keep the floor from pushing their knees around when they land from a jump. Girls tend to use their quadriceps—the large muscle group on the front of the thigh—a practice that actually puts more stress on the ACL. In addition, Hewett found, injuries tend to happen when the athletes put all of their weight on a single leg or foot.

"The good news," Hewett says, "is that we can address each of these things." He gives the girls exercises to increase the strength of their hamstrings. He videotapes them or has them train in front of a mirror so they can see what they're doing—for example, letting their knees collapse inward when they land from a rebound—and learn to avoid it. He also has them practice balancing, hopping and even squatting on one leg at a time to build up strength on both sides. "It's great exercise," Hewett says, and the benefits go beyond the basketball court. Most of us have muscular imbalances between our left and right sides, which is a risk factor for hip fracture, he points out. "So any way you can make yourself more symmetrical, your overall health is going to improve."

For osteoarthritis, Hewett says that preventing injury, especially to the ACL, is the way to go. "Our current treatments lead to as high or higher a rate of osteoarthritis than leaving things alone," he says. "So right now the only treatment that's shown to be efficacious is prevention." —*K.H.*

JASON LEE

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ANY SPORT THAT INVOLVES BODY CONTACT, JUMPING OR PIVOTING **RAISES A PLAYER'S RISK** OF OSTEOARTHRITIS.

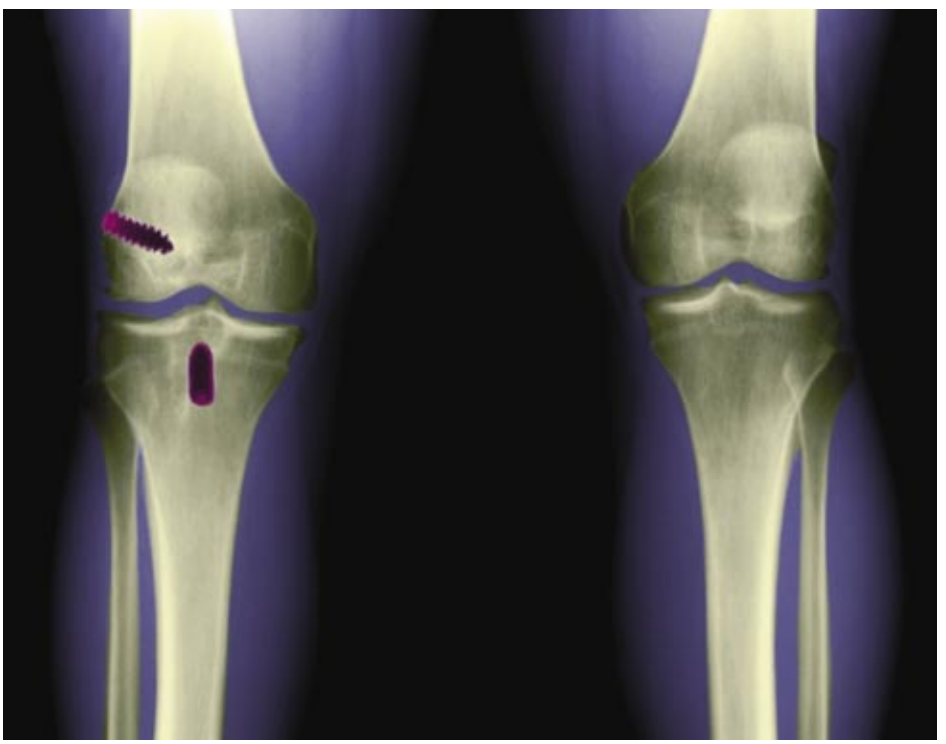
University School of Medicine. "Everyone is at risk." And treatment often involves complete replacement of the knee joint with a prosthetic device that, unfortunately, can also wear out over time.

Given those statistics, bioengineers and orthopedic surgeons are working to come up with new methods and materials for repairing worn-out ligaments and other joint components biologically—so that people in their 40s, 50s and even 60s can delay or avoid replacing their knees with metal or ceramic prostheses. In the clinic and in the lab, these researchers are exploring promising approaches to relieve pain, restore motion and encourage damaged joints to heal themselves.

Soccer players are among the athletes most at risk for osteoarthritis later in life.

ANATOMY OF AN INJURY

Every joint in the body is subject to damage, but the knee is the best studied, perhaps because it is "often injured and reasonably easy to diagnose," says Stefan Lohmander, an orthopedist who specializes in osteoarthritis at Lund University Hospital in Sweden. Knee injuries send a large portion of the population limping to the physician with complaints of pain and reduced mobility in that joint—problems that Lohmander notes can make "getting around, going shopping, seeing friends and participating in life difficult."



X-ray image compares a patient's knees, one of which received an ACL graft. Visible at the left are the screws used to hold the ends of the ligament graft in place.

The ACL is not the only structure in the knee that can cave under pressure. A few people snap the posterior cruciate ligament, which crosses the ACL in the center of the joint (hence the term "cruciate," for "cross-shaped"). Another structure that is subject to wear and tear is the articular cartilage, which covers the ends of the thighbone (femur) and shinbone (tibia) like a thick coat of paint. This slippery material (think of the white stuff on the end of a chicken drumstick) not only decreases the friction between the moving parts of the joint—allowing the bones to slide over one another—but serves as a cushion to evenly distribute the load that is introduced with each step. Lose this cartilage, and bone will rub on bone. Additional shock ab-

PHOTO AND CO./GETTY IMAGES (*top*); NEIL BORDEN *SPL/Photo Researchers, Inc.* (*bottom*)

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sorption in the knee comes from the meniscus, a washerlike wedge of cartilage that rests between the femur and the tibia. This structure—really a pair of structures, one on the outer half of the knee, one on the inner half—can also be damaged or torn by injury. When the meniscus is damaged, the articular cartilage underneath it can begin to wear; this combination of injuries can pave the way for osteoarthritis, with its associated inflammation and pain.

Any sport that involves body contact, jumping, landing, pivoting or zigzagging raises the players' risk of injury and osteoarthritis, particularly when athletes get back in the game before a damaged joint heals. Most at hazard are those who play soccer, football, basketball or tennis and those who perform gymnastics.

Women are particularly susceptible to tearing an ACL [*see box on page 65*]. "Women's gymnastics has as high a rate of ACL injuries as men's spring football," which is when collegiate teams practice and play scrimmage games, says Jennifer Hootman, an athletic trainer and epidemiologist with the Centers for Disease Control and Prevention. In Norway, which often takes home the trophy in women's team handball competitions, Hewett says "something like one in five women who play that sport tears her ACL."

"GIMME A GRAFT!"

For torn ACLs, treatment generally involves "trying to connect the knee back together in some way," Fu says. In the 1950s surgeons tried to stitch together the torn ends of the ACL. "Unfortunately, that didn't work too well," says Martha Murray, head of the sports medicine research laboratory at Children's Hospital Boston. Patients with sewn-up ACLs would eventually find that their knees were as unstable and prone to buckling as before the repair.

Of course, not everyone with a torn ACL needs surgery. "If you are not very active, if your lifestyle is such that you go swimming and walking but don't engage in activities that require sharp changes in direction—like basketball or tennis—you may be able to live without surgery," Fu says. Such individuals might be able to get by merely with physical rehabilitation to strengthen their leg muscles and help stabilize the joint.

Inflammation in this medical scan of a diseased knee is highlighted in red.

Nowadays people who opt for surgery usually receive a graft to stand in for the torn ligament. The surgeon removes the damaged ACL and replaces it either with a strip of the patellar tendon (a tough tissue that connects the kneecap to the tibia) or with the hamstring tendons (which attach the muscles on the back of the thigh to the tibia). Another option increasingly popular with elite athletes is to use an allograft—tissue from a cadaver. "I keep hearing at national and international meetings that surgeons who take care of professional sports teams—including basketball, football and soccer—are now using allografts as a first-line choice for ACL repair," says Andrew Chen, team physician for the U.S. Ski and Snowboard Association and an orthopedic sports medicine surgeon in Littleton, N.H. Although allografts actually take a longer time to integrate into the body after reconstruc-

GRAFT TENDONS MUST BE HEALTHY AND STRONG. LACK OF A SUITABLE ONE CAN SOMETIMES **POSTPONE SURGERIES FOR WEEKS**. TO GET AROUND SUCH PROBLEMS, KEVIN STONE IS TURNING TO PIGS.

ALAIN PDL ISM/SPL/Photo Researchers, Inc.

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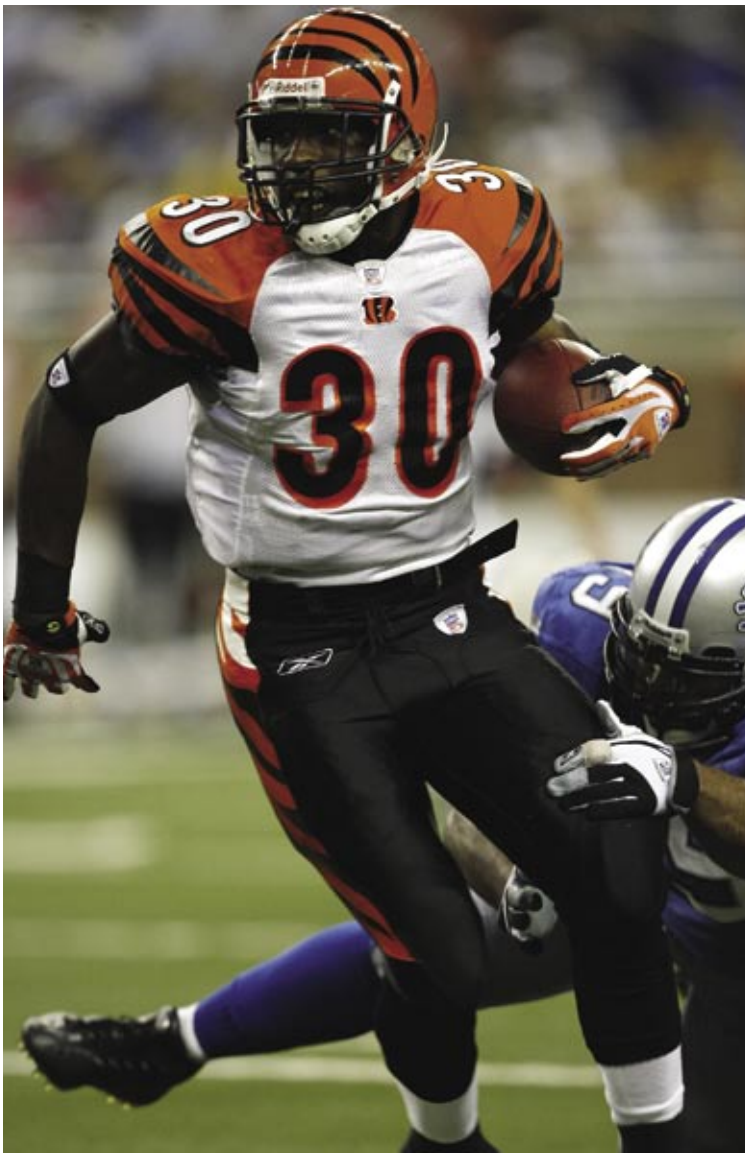

Cincinnati Bengals running back Kenny Irons tore the ACL in his left knee in August and has consequently had to sit out the 2007 season. He is expected to make a full recovery.

JOE ROBBINS Getty Images

tion, recipients may feel like the recovery time is shorter because they do not need to deal with the additional pain from where their own tendon was harvested. With so many high-profile players onboard, "a lot of athletes are saying, 'Put in an allograft, and if I blow it out, we can always put in another. This is my time to shine,' " Chen remarks.

Of course, allografts don't grow on trees. Although they do not need to be "matched" the same way a transplanted organ does, graft tendons must be healthy and strong, and thus they tend to come from donors somewhere between 18 and 35 years old. Lack of a suitable graft can sometimes postpone surgeries for weeks or months. To get around those problems, Kevin Stone, an orthopedic surgeon in San Francisco, is turning to pigs. "Pig ligaments are similar to human ligaments, and we can get them young, healthy and strong every time," he says. He and his colleagues have developed a method for stripping the porcine tissue of the proteins that would trigger rejection and have shown that the grafts are safe for use in humans. One individual in their initial safety study went on to win the Canadian masters downhill ski championship—three times.

A LONGER, BETTER SURGERY?

Regardless of where a graft comes from, Fu says surgeons need to pay more attention to where the graft goes: in other words, they should look to each patient's particular anatomy to determine where to anchor the new ligament to the bone. The traditional procedure—called a single-bundle replacement—involves simply attaching one end of the graft to the femur and the other end to the tibia.

But Fu argues that the current approach only does half the job, because the human ACL is actually made of two bundles: one that stabilizes the knee as it bends; the other that stabilizes the knee as it rotates. To restore normal anatomy—and range of motion—Fu says surgeons need to "connect A to A and B to B."

Convincing his colleagues, however, has been an uphill battle—in part because a double-bundle replacement takes longer to perform. "Fifteen years ago I would do an ACL in 30 minutes: bang, bang, bang, no problem," Fu notes. "But looking back, I see that what I did before this double-bundle procedure was quite crude."

Odd as it might seem, Fu's curiosity about the function of the human knee is what led him to operate on Johnny the mandrill. Fu was probing the monkey's knee for insight into the anatomy and mobility of animal ACLs, information that he hopes will help surgeons see that different parts of the ligament serve different purposes—and that all parts need to be restored for the joint to function properly. Johnny's ACL, it turns out, has three bundles, which give his knee an even greater ability to rotate—a feature that Fu thinks

"ATHLETES ARE SAYING, 'PUT IN AN ALLOGRAFT, AND IF I BLOW IT OUT, **WE CAN ALWAYS PUT IN ANOTHER,**'" ANDREW CHEN SAYS.

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AN ACL, ONCE TORN, **CANNOT MEND ITSELF**, SO SOME SCIENTISTS ARE TRYING TO COME UP WITH MATERIALS THAT CAN BRIDGE THE GAP.

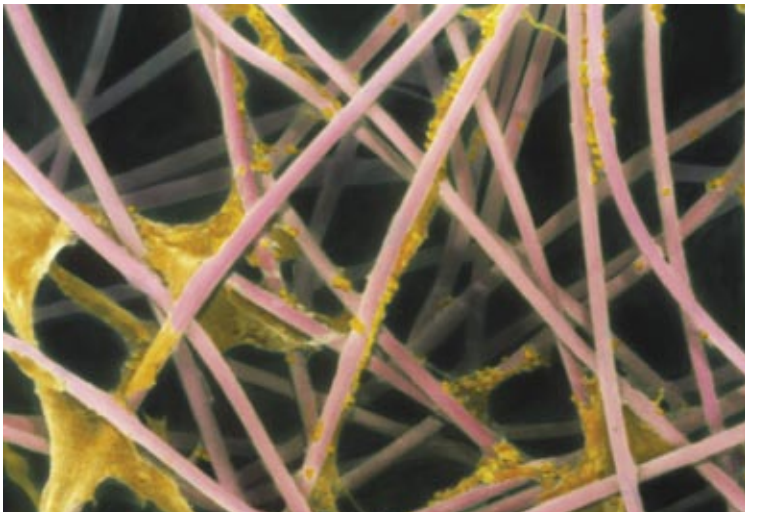
might come in handy when the monkey is reaching for a tree branch to get to some ripe fruit or running from a bigger monkey.

ENTER THE BIOREACTOR

An ACL, once torn, cannot spontaneously mend itself—in part, Murray says, because "there's no structure for the cells in the stumps to crawl into to build a new ligament." So some researchers are trying to come up with materials that can bridge that gap, allowing the ACL to regrow. Murray is betting on the blood cells called platelets. She has produced a platelet-rich gel that she squeezes into the space that remains when a torn ACL is sewn back together. The mixture forms a clot, which promotes the formation of scar tissue—the same way platelets help to heal a cut in the skin. In experiments with pigs—published in the *Journal of Orthopaedic Research* in January 2007—Murray reports robust healing: at four weeks the repair has regained 40 to 50 percent of the strength of an intact ACL. Preliminary results for later in the healing process show blood vessels growing into the new tissue and cells dividing and producing collagen—one of the main components of a ligament.

The results are particularly encouraging, considering the patients. "The pigs feel good enough within a couple days that they're up walking around and standing on their repairs," Murray says. Yet despite the lack of couch time and crutches, the pigs' ligaments appear to heal. "That makes us hopeful that when we get to clinical trials, where we have more control over the patients, the results will be even better," she says. "Although with some of my teenage patients, I'm not sure how much control I really have."

Greg Altman, president and CEO of Serica Technologies in Medford, Mass., is taking a similar approach, co-opting the body's natural repair capabilities to mend a wrecked knee. In studies with goats, instead of sewing the loose ends back together, Altman and his colleagues remove the damaged ACL entirely and replace it with a scaffold made of silk. This material is strong enough to support the growth of a new ligament, and the researchers have treated the fiber so that the body degrades it over time, leaving a strong new ACL in its place. The results of Altman's studies—presented at the annual meeting of the American Orthopaedic Society for Sports Medicine in July 2007—look good: the ACL regrows, the repaired joint is stable and, after 12 months, the researchers see no signs of arthritis. "We observed a very calm, intact joint," says Altman, who is initiating a clinical study in Europe to test the safety and effectiveness of the grafts in patients.



Artificially grown cartilage (*orange*) on biodegradable fibers (*pink*) might someday be used widely to repair joint linings.

Best of all, the silk graft needs no special storage or refrigeration, so a surgeon should be able to size a patient's joint and literally pull a replacement off the shelf. Avoiding the need for harvesting grafts from the patient's own knee was an important consideration in the development of the silk scaffold, says Altman, who tore his own ACL as an offensive lineman during his senior year at Tufts University and received a graft from his patellar tendon to take its place. "My ACL was pretty good," he recalls, "but my patellar tendon was killing me." The experience drove Altman to enroll in graduate school—initially so that he could play a fifth year of football but also so he could help other people recover better from ACL injury.

GREEN TEA ON THE KNEE

Athletes like Altman who have torn an ACL are perhaps 10 times more likely to develop osteoarthritis than folks in the general population, according to Lohmander. But they're not the only ones at risk. Arthritis tends to run in families, so genes play a role. So does obesity and even aging itself. Currently no treatments cure the disease. "We have drugs, like painkillers and anti-inflam-

DAVID MOONEY *SPL/Photo Researchers, Inc.*

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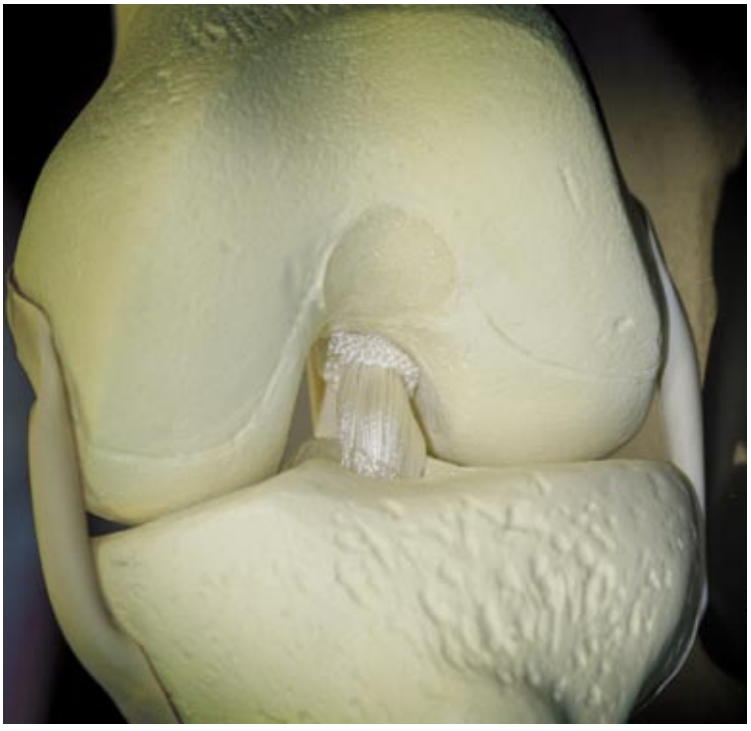

A silk graft being developed by Serica Technologies as an ACL replacement should be available in the next five years.

matory agents, that alleviate the symptoms," Lohmander says. "But there's nothing that really stops or slows down the development of osteoarthritis once it starts."

Of course, alleviating pain is nothing to scoff at. For some patients, a course of injections of hyaluronate—a molecule normally found in the synovial fluid that keeps the knee joint lubricated—can offer dramatic pain relief. Although the best results are seen with people who have mild to moderate arthritis, even those with severe arthritis may find the treatment worth a shot. "I've had patients who were told that nothing more could be done for them save for a total knee replacement," Chen says. "But they come to me every six months for a series of three injections, and they love it. It makes their knee feel great, and they can go out and do the things they want to do."

Unfortunately, as the disease progresses, the damage mounts, and many people with osteoarthritis wind up having a knee replacement. The substitution relieves pain and restores mobility, making it "one of the most successful operations in medical history," says Joseph Buckwalter, an orthopedic surgeon and researcher at the University of Iowa Hospitals and Clinics. But the approach has its drawbacks, including the fact that the implants can wear out with time, just as "the tires on your car wear out when you drive or your shoes when you walk," Lohmander says.

While prostheses continue to improve—current devices last 20 years or more, and orthopedics manufacturer Zimmer in Warsaw, Ind., recently introduced an artificial knee designed specifically for women—researchers keep searching for more biologically friendly ways to rejuvenate an arthritic joint. Buckwalter and his colleagues have found that as people age, the cells that maintain the knee's articular cartilage begin to fail. The cartilage then weakens, which makes the knee more vulnerable to injury and mechanical malfunction. Treating isolated strips of cartilage in the lab with antioxidants—including purified extracts of green tea—appears to revive those exhausted cells and to prevent or minimize mechanical damage to the joint, Buckwalter says.

BEYOND POTHOLES

Although a whole knee can be replaced, damaged cartilage alone can't be fixed by swapping in something synthetic. "The knee goes through two to three million steps per year from normal walking and experiences up to five times the body weight, depending on the height of the step," Stone says. "There's no artificial material known to man that you can put in the joint that won't either damage the opposing side or wear down rapidly."

"THERE'S NO ARTIFICIAL MATERIAL KNOWN TO MAN THAT YOU CAN PUT IN THE JOINT THAT WON'T EITHER DAMAGE THE OPPOSING SIDE OR WEAR DOWN RAPIDLY," STONE SAYS.

Hence, surgeons have devised a variety of techniques that use some of the patient's own tissue to repair small areas of cartilage damage—nicks, tears or holes that arise from a blow to the knee or some other localized injury. The most common approach involves harvesting a piece of the patient's cartilage and sending it off to a commercial laboratory that multiplies the cartilage cells in a culture dish and ships that expanded material back to the surgeon, who then uses it to patch the knee damage—"sort of like filling a

SERICA TECHNOLOGIES

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TREATING ISOLATED STRIPS OF CARTILAGE IN THE LAB WITH ANTIOXIDANTS APPEARS TO **REVIVE THOSE EXHAUSTED CELLS.**

AGE FOTOSTOCK

Staying active and stretching are important for preserving the flexibility and fitness of joints, not to mention overall well-being.

pothole," says Farshid Guilak, a bioengineer at Duke University Medical Center.

Guilak is replacing more extensive regions of damaged cartilage by developing stem cells, which have the ability to produce new cells of other types of tissue. The stem cells he uses are a versatile variety harvested from liposuctioned fat. He and his colleagues spread these stem cells over a specially designed woven polyester scaffold. They then bathe this cell-studded material with growth factors that coax the cells to produce cartilage. So far it looks like the cells are up to the job; Guilak and his lab are gearing up to test the scaffold in the hip joints of goats.

In the meantime, Buckwalter and others continue to work on imaging techniques that will allow them to identify molecular changes to the cartilage that could herald impending deterioration. Whether such tools will help surgeons head off osteoarthritis or other potential problems in those who may be at risk, Felson acknowledges, "is unknowable right now."

As for Johnny the mandrill, Fu was able to remove some of the scar tissue and inflammation that was causing his patient's discomfort—which is where he intends to leave things for now. "I don't think anybody in the world has ever reconstructed an ACL in a monkey," Fu says. "I don't pretend I know how to do it." Meanwhile the patient is doing well, enjoying extra helpings of pudding and bananas. ■

KAREN HOPKIN, a Boston-area writer who covers science and medicine, regularly contributes to *Scientific American*'s *60-Second Science* podcasts at **www.SciAm.com**

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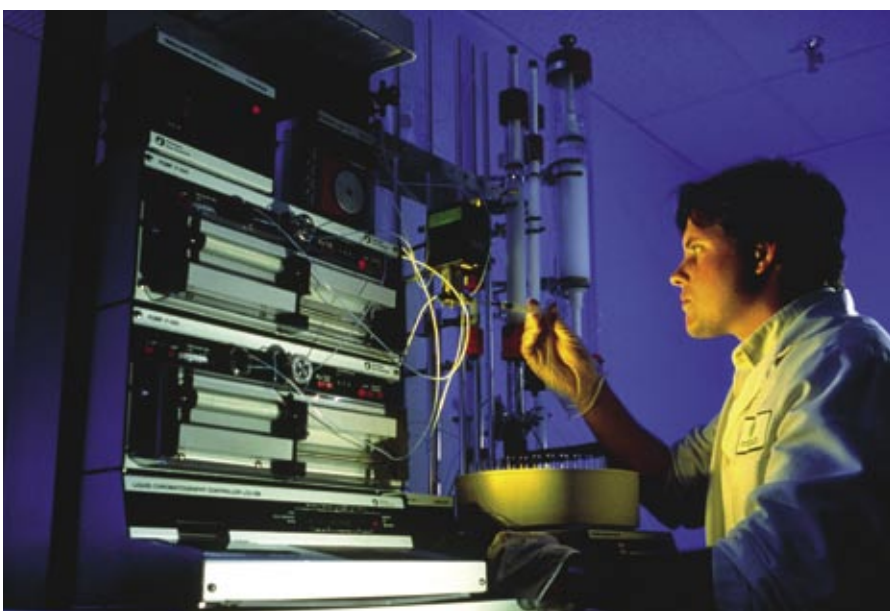

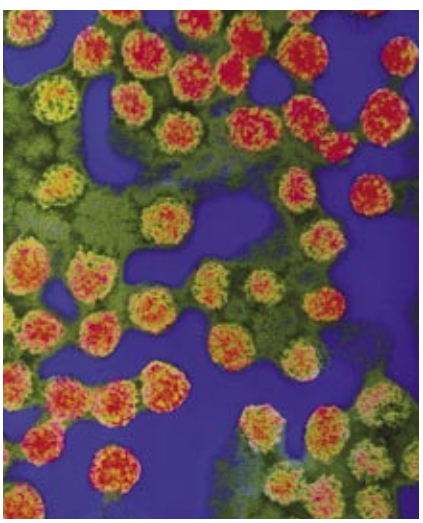

Despite two decades of work, researchers have not been able to create a satisfactory vaccine against HIV.

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SCIENCE GETS CLOSER, BUT A FULLY EFFECTIVE VACCINE AGAINST HIV REMAINS ELUSIVE

By JR Minkel

Ten years ago President Bill Clinton set a national goal to develop an AIDS vaccine within a decade. At that time, the human immunodeficiency virus (HIV) that causes AIDS had infected some 25 million people worldwide. Clinton established a research center at the National Institutes of Health and pledged to enlist other nations in the effort.

"There are no guarantees," he said in a speech delivered at Morgan State University announcing the initiative. "It will take energy and focus and demand great effort from our greatest minds. But with the strides of recent years, it is no longer a question of whether we can develop an AIDS vaccine, it is simply a question of when."

Infectious disease experts cautioned that the goal was overly optimistic. They were right. Today there is still no vaccine, despite an increasingly organized global effort and the quadrupling of funds committed to it. "We have learned in that period of time how formidable an adversary HIV is," says Wayne Koff, senior vice president for research and development at the International AIDS Vaccine Initiative (IAVI).

The vaccine search suffered its latest disappointment in September, when investigators called an early stop to a clinical trial of a much anticipated new type of HIV vaccine. Like many other candidates now in testing, it was designed to coax the immune system's disease-killing T cells into attacking the virus more aggressively. Experts say that such a vaccine is unlikely to prevent HIV infection. But they hope at least one candidate will weaken the virus enough to delay the complications of AIDS and to reduce the need for expensive antiretroviral drugs.

HANK MORGAN *SPL/Photo Researchers, Inc.* (*top and left*); NIBSC *Photo Researchers, Inc.* (*right*)

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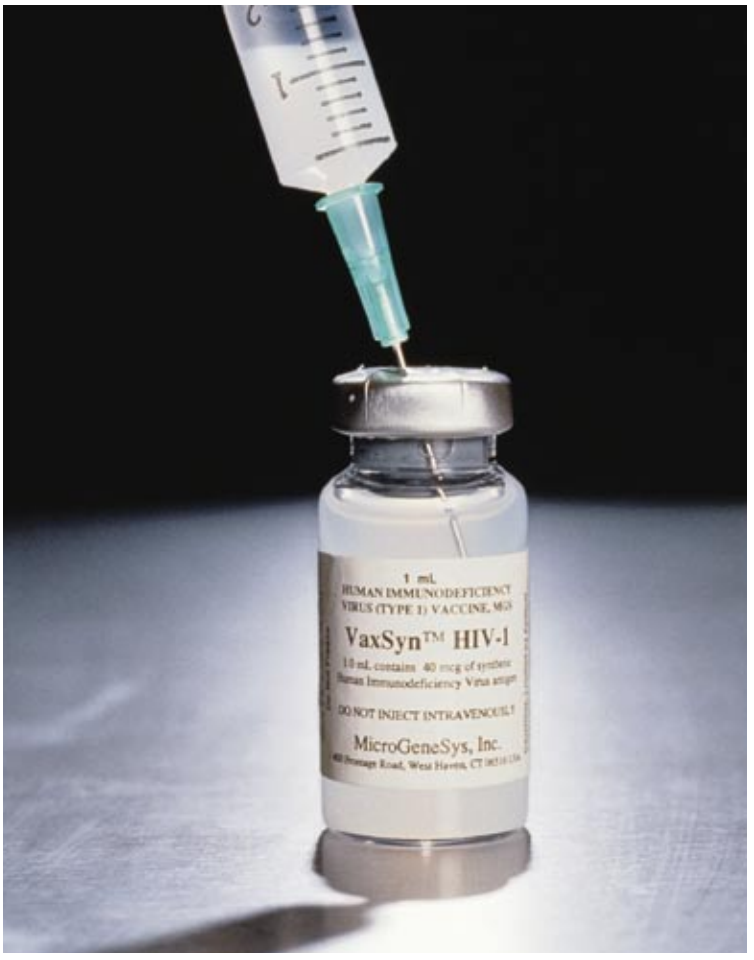

VaxSyn, an anti-HIV vaccine based on a viral protein called gp160, dates back to the 1980s. It was unsuccessful.

Increased funding and more sophisticated organization have played a key role in getting the project this far. "By the early to mid-1990s the AIDS vaccine effort was relatively moribund," says IAVI president Seth Berkley, who founded the group in 1996. "It's 100 percent a scientific problem; however, without an enabling environment, you can't solve the science."

Global spending for HIV vaccine research increased from $186 million in 1997 to $759 million in 2005, according to the Joint United Nations Program on HIV/AIDS. The IAVI helped to move the field forward by establishing research consortia so that investigators could more easily coordinate and exchange information. The group partnered with governments and vaccine makers to conduct trials outside the U.S., which account for nearly half of the 30-plus trials currently in progress. The NIH formed its own HIV vaccine trial network in 2000 to oversee clinical research sites in the U.S., Africa, Asia, the Caribbean and South America.

The scale of the effort reflects the scientific challenges. In the early 1980s, after identifying the HIV virus as the cause of AIDS, researchers were at first confident that they could come up with a vaccine against it within a few years, Koff says. Vaccines work by exposing the body to a disease-causing agent or a fragment of it. That exposure primes the immune system to produce a flood of antibodies that stick to the infecting organism and block it from entering cells. Researchers identified a protein on the surface of HIV, dubbed gp120, that enables the virus to infect and then slowly destroy so-called helper T cells, which regulate immune responses. The gp120 protein seemed like a good candidate for an HIV vaccine.

And early tests of a gp120 vaccine looked promising. But optimism faded by the early 1990s as researchers learned the vaccine worked only against strains of HIV that had adapted to conditions in the laboratory. In 2003 results finally came in from a phase III clinical effectiveness trial of a gp120 vaccine manufactured by VaxGen: it failed to prevent infections or reduce the number of virus particles circulating in the blood. (A related vaccine, VaxSyn, based on the gp160 protein [*see illustration at left*], never progressed to late-stage clinical testing.)

By then, HIV researchers had turned to a different idea for a vaccine. They inserted segments of HIV genes into the DNA of partially disabled non-HIV viruses. The resulting viruses could deliver the HIV genes into cells without causing a lethal infection. Infected cells would produce and display HIV proteins, however—thereby energizing the immune system's T cells to attack those proteins wherever they might appear.

Merck, along with the federally funded HIV Vaccine Trials Network (HVTN), initiated a phase II clinical proof-of-concept trial in late 2004 to quickly study the effectiveness of its adenovirus-based vaccine containing three HIV genes. In September a peek at the data revealed that participants injected with the vaccine had contracted HIV no less often than had those receiving a sham. Investigators halted the study, which had enrolled 3,000 people in the Americas and Australia, as well as a second trial begun in 2006 in South Africa. In the coming months, researchers hope to figure out why the vaccine failed and how to improve the remaining crop.

Next up for rapid testing is a broader-spectrum vaccine developed by the NIH's Vaccine Research Center (VRC). Sanofi-Aventis is conducting a phase III clinical trial in Thailand of its product, which combines a canarypox virus vac-

HANK MORGAN *SPL/Photo Researchers, Inc.*

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cine with VaxGen's gp120 vaccine. Results are due as early as 2008.

"The immune response and the safety so far have put these out there further than the other candidates we have," says disease specialist Scott Hammer of Columbia University, part of the team designing the VRC vaccine trial.

Studies in monkeys seem to support the concept, says immunologist David Watkins of the University of Wisconsin–Madison. Watkins and his colleagues reported in 2006 that rhesus monkeys injected with four genes from the simian immunodeficiency virus—which causes an AIDS-like disease in monkeys and apes—were no less susceptible to infection by the identical strain of the simian virus than were unvaccinated monkeys, but they did maintain lower levels of virus in their blood for up to a year after infection. Another group reported that vaccinated monkeys were more likely to survive three years after infection than unvaccinated animals were. "That was pretty encouraging," Watkins says. But he cautions against putting too much weight on the early results.

The ability of HIV to mutate rapidly remains one of the biggest obstacles to a successful vaccine. Its genetic material is prone to errors during duplication and replicating HIV molecules frequently exchange pieces of genes. Because of this instability and the potentially rapid life cycle of the virus, the genetic sequences of HIV particles in a single person can be as diverse as those of all the influenza viruses in the world. A vaccine that produces an immune response against one HIV sequence may have no effect on other strains.

To address this problem, the VRC vaccine contains three variants of the HIV envelope gene—the gene that most readily mutates to resist treatment. The HVTN began a second trial of Merck's vaccine last February in South Africa, where the circulating virus differs from the one on which the vaccine is based.

T cell–stimulating vaccines may help destroy cells infected with HIV, preventing them from reproducing. But experts say they probably would not trigger the immune system to make antibodies and would therefore be only partially effective. "You're trying to control replication, not prevent infection," Watkins says. "Although, who knows? Maybe a T cell vaccine could do that."

Merck and the HVTN called their test "STEP," because a successful T cell vaccine would be only a step toward full protection—but it could be a highly significant one. The IAVI estimates that even a 30 percent effective vaccine given to just 20 percent of those at risk would avert 5.5 million infections worldwide between 2015 and 2030—or 11 percent of all estimated new infections for that period. A 70 percent effective vaccine administered to twice as many patients could avert 28 million infections.

Still, there are no guarantees. "We should never assume that what we have is going to work," says Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition in New York City. "We've got some very good candidates," the IAVI's Berkley adds, "and if they work it's going to be about access" for developing countries. "We have to make sure there's going to be the political and financial commitment to drive this effort forward, no matter the results of these trials."

In the future, researchers hope to find new candidates for antibody vaccines. A few people, when infected with HIV, spontaneously generate antibodies that can fend off the virus for decades. Researchers are studying the structure of these natural molecules. The IAVI established its neutralizing antibody consortium in 2002 to speed the discovery of triggers that would prod the immune system to generate more of them.

After 10 years of research, experts are in a better position to judge their expectations for the future. The consensus: a fully effective AIDS vaccine is a long way off. "There are people who will tell you we will never have a vaccine—I can't say those people are wrong," Hammer says. But he adds that "you shouldn't be in this business if you don't have some degree of optimism based on the science. The world needs an AIDS vaccine. To give up now is selling the science short." ■

JR MINKEL is a news reporter for SciAm.com, the Web site of *Scientific American*.

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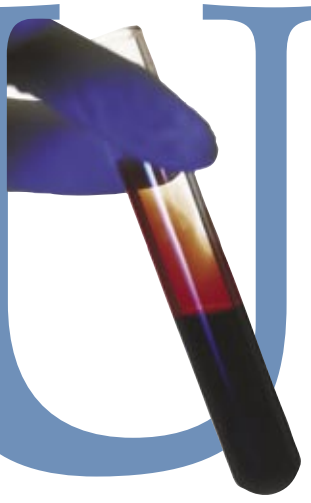
The Ultimate Blood Test



VICTOR HABBICK VISIONS (*left*) AND MAURO FERMARIELLO (*above*) *Photo Researchers, Inc.*

A PRICEY WAY TO DETERMINE HEALTH RISKS: **250 TESTS AT ONCE**

By Philip Yam

As the dizziness began to fade and the nausea to subside, I kept thinking how two tablespoons did not sound like a lot of blood. During regular checkups, my physician draws only about half that amount. I suppose I might have guessed, especially after a 12-hour fast, I would sicken when my blood pressure and glucose levels dipped—I'm a terrible blood donor in that regard.

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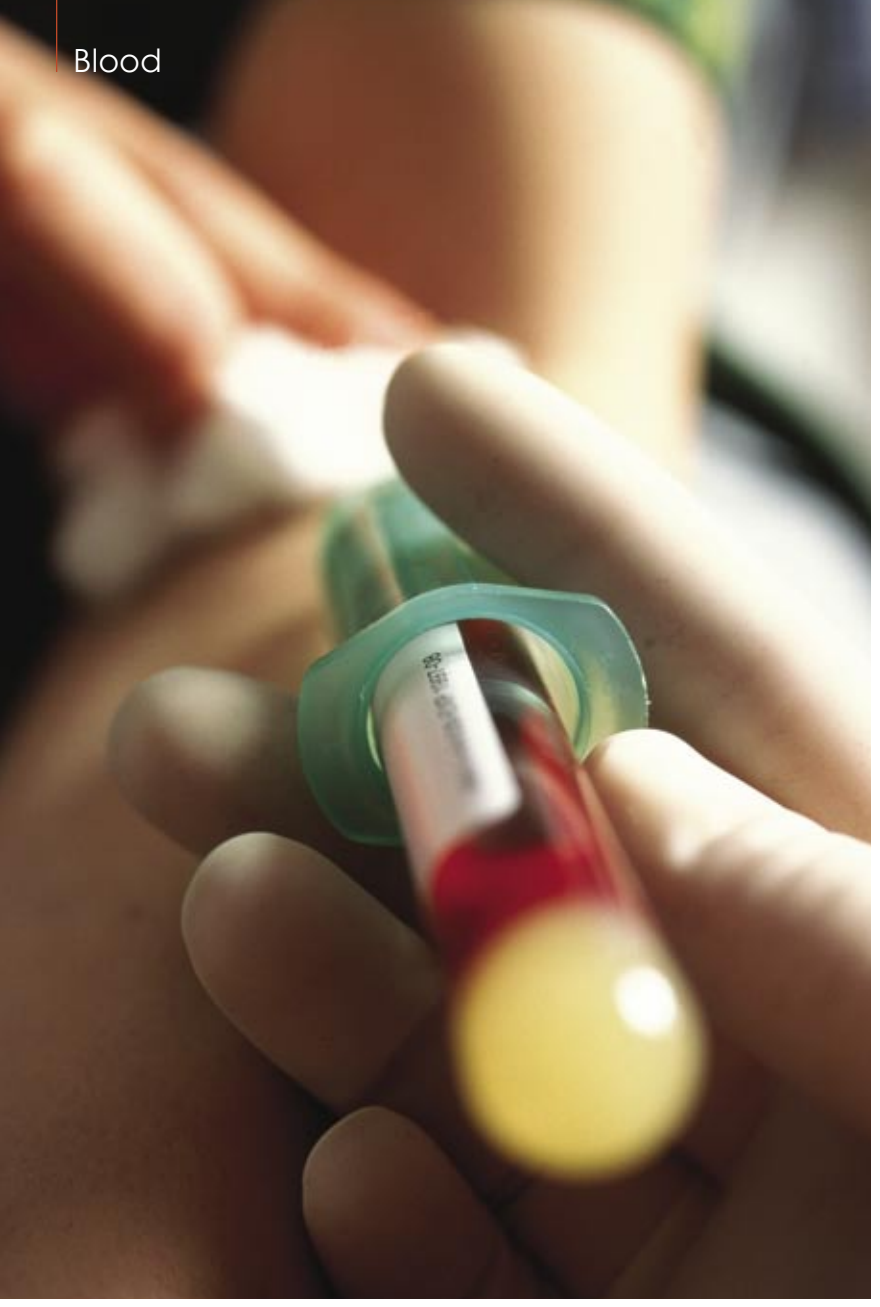

Two tablespoons of drawn blood are sufficient for a battery of tests.

The nurse who drew my blood helpfully looked around my office for a sweet drink. "Do you have any soda or juice?" she asked. But the only thing I had was a can of Diet Coke. Which in a way is ironic: I used to drink regular Coke but switched to the sugar-free form after blood tests revealed that my triglycerides were too high.

Momentary ill feelings, though, were an acceptable physical price for 250 blood tests done at once—I was told that running them separately with conventional means would require a liter of blood. (Imagine how dizzy and nauseated I'd feel then.) So how could I not roll up my sleeve for Biophysical Corporation? The Austin, Tex.–based company promised to use the blood to screen for presymptomatic cancers, potential immune disorders, latent infections, undetected hormonal imbalances and unrecognized nutritional deficiencies. It seemed to mark a step toward that *Star Trek* future in which Dr. McCoy waves around a device shaped like a saltshaker to determine a person's medical secrets. ("Heartbeat is all wrong. Body temperature is ... Jim, this man is a Klingon!")

The Biophysical250 assessment, as the firm calls it, is more than just a battery of tests. It includes a medical-history interview; a personal visit to the home or office for the blood draw (I should have picked my home, where I actually keep sugar); and a follow-up physician consultation. All this attention does not come cheap. It costs $3,400 and is not covered by health insurance. The company states that doing each test individually would cost 10 times more, so the Biophysical250 is a bargain by comparison. Still, you either need some disposable income or must be so indispensable to your employers that they will pay for it. I don't fall into either category. But because I was reviewing its product, Biophysical agreed to conduct the test on me for free.

The analysis focuses on blood biomarkers, which are chemicals whose presence or amount may indicate abnormal processes or reactions in the body. Among the most familiar are cardiovascular ones: high- and low-density lipoproteins (HDL and LDL, the good and bad cholesterols) and triglycerides.

Checking 250 biomarkers at once might seem like overkill. A routine exam screens for two or three dozen. Looking at one biomarker in isolation, however, is usually not especially informative—for instance, the ratio of LDL to HDL is more important than either alone. The Biophysical250 takes it much further: to assess the risk for heart disease and stroke, the firm analyzes 33 biomarkers.

Examining several biomarkers together improves the odds of finding problems early, especially malignancies. Blood tests for cancers have been problematic, because healthy people may produce the same kinds and amounts of the biomarkers that cancer patients do. Moreover, the chemicals do not always show up in cancer patients, and they may result from unrelated conditions. The Biophysical250 screens for about four dozen blood chemicals tied to cancerous activity in general to increase the odds of detecting disease before symptoms appear.

For example, Biophysical points to ovarian cancer, which is usually diagnosed too late. Cancer antigen 125, the most commonly measured marker for the disease, shows up in only half of

PETER CADE *Getty Images*

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EXAMINING SEVERAL BIOMARKERS TOGETHER IMPROVES THE ODDS OF FINDING PROBLEMS EARLY.

patients in stage 1, when treatment is most likely to succeed. The Biophysical250 tries to boost the chance of early detection by measuring other, biologically independent compounds, such as vascular endothelial growth factor, interleukin-6 and monocyte chemoattractant protein.

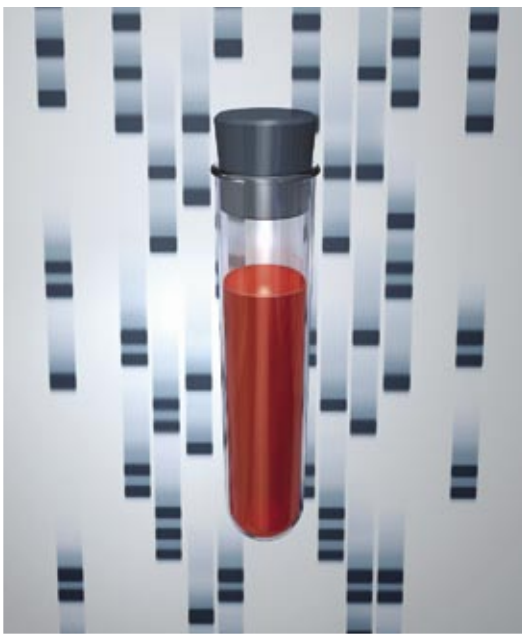
Some physicians have complained about the test, arguing that looking for so many biomarkers is bound to uncover many out-of-range values in perfectly healthy individuals. That is true, but it misses the point: the test looks at the biomarkers in combination, not in isolation, so that the relative biomarker levels serve as the basis for diagnoses. "Just the fact that we stack so many biomarkers really minimizes false positives," comments Mark Chandler, CEO and founder of Biophysical.

The firm has basically miniaturized the standard blood tests through the use of tiny polystyrene beads, each about half the size of a red blood cell. Each sphere is coated with a particular antibody. (Antibodies are disease-fighting agents made by the immune system that recognize specific protein molecules, typically from invading microbes.) The serum from the blood sample mixes with the beads for 15 to 30 minutes, allowing the antibodies to grab onto the proteins they recognize. After the serum is washed away, another of the same set of antibodies goes in. This time, though, each antibody also has a fluorescent tag. The tagged antibodies sandwich the blood proteins already held by the first set of antibodies. Examining the fluorescent tags thus provides "an idea of how much of the chemical was pulled out of serum," explains Chandler, who began selling the Biophysical250 assessment in 2005.

My report arrived two weeks later via FedEx. It included a well-written summary plus a quantitative laboratory report. A second booklet defined all the biomarkers and the ailments with which they correlated. In terms of health, the most useful part is the summary of biomarkers organized by type: autoimmune, cancer, cardiovascular, cell signaling, diabetes, endocrine, hematology, immune/inflammation, infectious disease, nutritional, organ systems and osteoarthritic. Next to each biomarker was a color code, depending on whether the detected amount was out of range: green for "low risk," yellow for "caution" and red for "alert." The report also came with a copy to give to my personal physician; Biophysical will discuss the results with a client's doctor. I also later had a telephone consultation about my results with George Rodgers, the company's president and cardiovascular specialist.

My results were mind-numbingly normal. Most everything came up green. The only surprise was my slightly out-of-range ferritin, a protein that stores iron. My report warned me that such iron overload might signal a genetic condition called hemochromatosis. The disease progresses silently and can cause toxic levels of iron to build up in organs. The treatment is simple: regular blood donations to drain off the excess iron. On the other hand, my ferritin level might reflect the fact that I had been taking a multivitamin with iron—a no-no for healthy men, I later discovered. I stopped, and when I had my regular physician check my ferritin levels seven months later, they had dropped to within a normal range.

And therein lies a great strength of Biophysical250: it can uncover a presymptomatic, potentially fatal disease that physicians might not or-



DIGITAL ART/CORBIS

Chemical biomarkers in the blood can be clues to underlying genetic conditions.

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What Biomarkers Can Say about Health

According to Biophysical Corporation, the 250 biochemical markers measured by its assay provide information about a broad range of the body's organic systems and their state of function. The biomarkers can be accordingly assigned to different categories; some fit into several groupings simultaneously because those molecules play multiple important roles in sickness and health.

Autoimmune
Illnesses such as multiple sclerosis, lupus and scleroderma arise when the immune system turns its arsenal of disease-fighting molecules and cells against the body's own tissues. The test looks for antibodies that could react with cellular DNA and proteins.

Cancer
Malignancies are highly diverse, but their uncontrolled growth and the tissue disruptions they produce can show up as a shift in the makeup of the blood serum. Relevant biomarkers therefore include cancer-specific antigen proteins, various hormones, white blood cells (such as monocytes, neutrophils and eosinophils) and even certain viruses associated with tumors.

Cardiovascular
Levels of lipoproteins, triglycerides, cholesterol and other compounds—as well as the ratios between them—are risk factors for diseases affecting the heart and blood vessels, such as atherosclerosis. Because damaged cardiac muscle cells release creatine kinase, its presence can suggest that a heart attack has occurred.

Cell Signaling
The body's ability to heal itself and stave off disease depends on the chemical signals called cytokines with which cells communicate. Measuring those cytokines enables physicians to eavesdrop on that conversation for hints about the body's condition.

Diabetes
Measurements of the blood sugar glucose and of the hormone insulin, which regulates how cells use glucose, are giveaways for diabetes. Other factors can help reveal what type of diabetes is involved.

Endocrine
Hormones released by the endocrine glands (the pituitary, thyroid, parathyroid, adrenals, ovaries or testes, and others) regulate organ functions throughout the body. Imbalances in these secretions can be highly indicative of different disorders.

Hematology
Biomarkers in this diverse group reflect abnormalities in the volume of fluid or blood that the body maintains, which can relate to infections, anemia, clotting problems or allergies.

Infectious Disease
The test can look for evidence of bacteria and viruses that cause common diseases such as influenza, hepatitis, tuberculosis, chlamydia, Lyme disease or even gastric ulcers or for signs of parasites that cause leishmaniasis and trypanosomiasis (sleeping sickness).

Inflammation
Injuries from bacteria, trauma, toxins and other causes trigger the inflammatory response, which helps the body eliminate disease agents and damaged tissue. Inflammation biomarkers include various immunoglobulins, heat-shock proteins and other molecules.

Nutritional
Blood serum assays for calcium, cholesterol, sodium, vitamin B_{12}, iron, potassium and many other nutrients can detect current or imminent problems resulting from malnutrition.

Organ Function
Abnormal levels of key molecules in the bloodstream can mean that major organ systems are malfunctioning or at risk, especially if pathogenic organisms are also present. Among the biomarkers measured by the test are antibodies against hepatitis viruses (for liver problems), sodium and uric acid (for kidney ailments) and antibodies against *Helicobacter pylori* (the bacterium that causes gastric ulcers).

Osteoarthritis
Wear and tear on the joints can eventually lead to the painful inflammation of osteoarthritis. Early stages of the problem can be detected by looking for molecules such as C-reactive protein, rheumatoid factor and antibodies against the connective tissue collagen.

—The Editors

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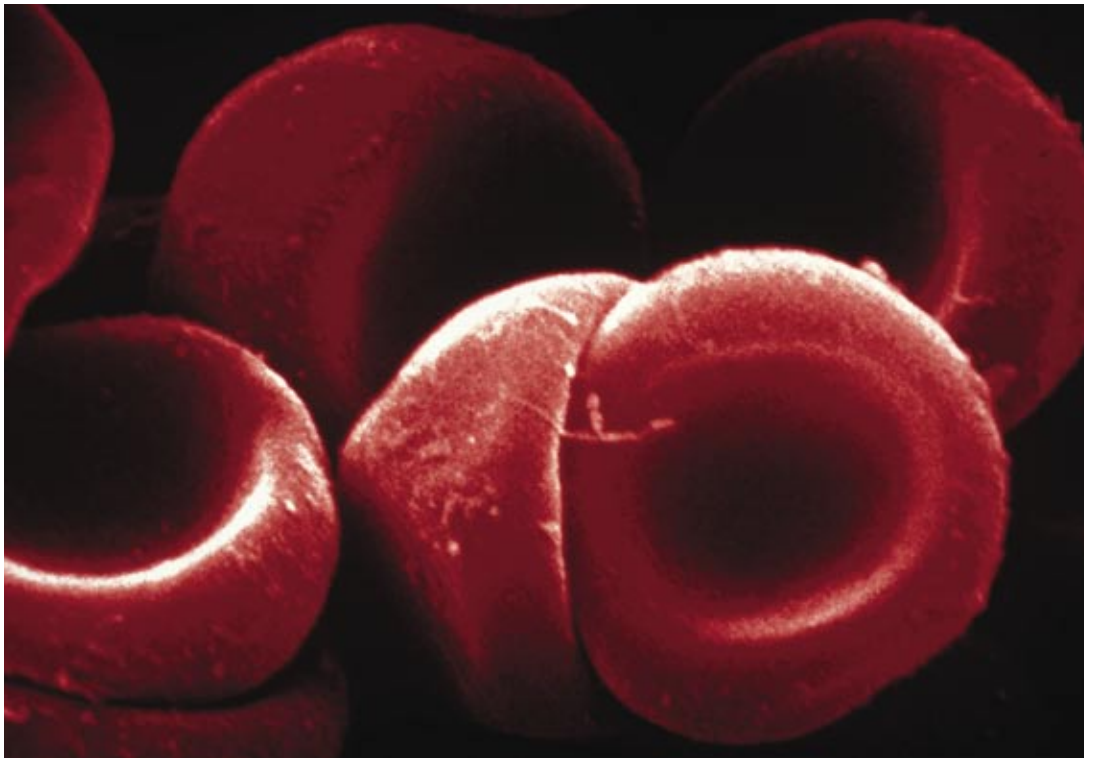
DID I REALLY NEED TO FIND OUT THAT I HAVE NO AFRICAN SLEEPING SICKNESS PARASITES?



RALPH C. EAGLE, JR. *Photo Researchers, Inc.*

Red cells, which ferry vital oxygen to tissues, are only the most visibly prevalent component of blood. The serum component is rich in proteins and small molecules that regulate health.

dinarily test for. The firm reports that in an unpublished study of 120 clients, 15 turned out to have major health risks and another 27 indicated moderate risks; none showed outward signs of disease. The conditions included rheumatoid arthritis, scleroderma and hypothyroidism.

The company screens only for treatable ailments and avoids those that are invariably fatal. (Why stress out patients with dire news or warnings that they can't do anything about?) So for now, neurodegenerative conditions such as Alzheimer's disease are out. But, Chandler adds, the firm would consider testing for such illnesses "if there's a way to slow down progression of the disease."

My Biophysical250 results were limited in the sense that they reflected my health on the precise day at the precise time when my blood was drawn. Biochemical changes over time, though, reveal more about the state of a person's health. But at the cost of a giant flat-screen plasma TV, the Biophysical250 is not exactly affordable, even if done every other year. Couldn't the company knock off a few of the tests? I mean, did I really need to find out that I have no African sleeping sickness parasites, considering that I've never been to Africa? Or to know that I am not pregnant?

Chandler says that plucking out a few of the beads would not be cost-effective, although perhaps a few dozen biomarkers might be enough to catch the most common afflictions and permit a less expensive assessment. He would like data from 10,000 clients before pruning the number of biomarkers. (He expects about 1,500 customers by the end of 2007.) The company may head in the other direction and institute a Biophysical300 as research uncovers more biomarkers. I'd certainly be game for it if the price came down—and as long as it does not need more than two tablespoons of blood. ■

PHILIP YAM is the news editor of *Scientific American*.

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5 New Year's Resolutions You Owe Yourself

WE QUESTIONED HEALTH PROFESSIONALS AND PLUMBED THE SCIENTIFIC LITERATURE IN A QUEST FOR THE MOST LIFE-ENHANCING NEW YEAR'S RESOLUTIONS POSSIBLE

By Charles Q. Choi

On New Year's Day more than a few of us annually resolve to change our lives—or at least our more self-indulgent habits. On the hunch that all good things flow from physical and mental well-being, *Scientific American Body* offers this list of recommended resolutions based on the advice of health professionals and the scientific literature. Whatever your goals, it will help you understand why hardly anything you could choose to do would have a bigger impact on your quality of life.

Perhaps the best New Year's resolution is coming up with a strategy to sen-

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AGE FOTOSTOCK (*fruit* and *cigarette*); GETTY IMAGES (*bicyclists*); WIDMANN/AGE FOTOSTOCK (*wine*); DARRYL LENIUK *age Fotostock* (*feet*)

sibly tackle each of the five listed below. "New Year's resolutions are notoriously unsuccessful because people have a superficial commitment to them," notes health psychologist Frederick Gibbons of Iowa State University. "Whatever behavior you want to change requires a specific plan for going about it."

For instance, to quit smoking or to moderate drinking, "people might want to plan ahead for situations or cues they need to avoid, since they may face social pressure, even if it's unintentional pressure. That might also include tempting foods," Gibbons says. Social support is also critical. Warren Franke, director of Iowa State's Exercise Clinic, believes that success toward an exercise or weight-loss goal could mean enlisting a significant other or a buddy to work out or diet with you or joining a formal program.

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IT'S THE ADVICE YOU HAVE PROBABLY BEEN HEARING FOR MOST OF YOUR LIFE. AND YET DESPITE THE WARNINGS, SMOKING IS STILL THE LEADING CAUSE OF PREVENTABLE DEATH IN THE U.S.

Controlling drinking may even require taking part in a behavior-modification treatment, Gibbons adds.

In pursuing these resolutions, set short-term goals, "such as losing just one pound a week," Franke says. If you sometimes find yourself sliding, "such as trying that killer cheesecake, don't feel bad about yourself and give up. Accept that was a bad day and that [the] next day will be a good day. And reward yourself. Life's too short not to enjoy it. Don't buy yourself six scoops of Ben & Jerry's, mind you. I have a friend who, if she's lost weight, buys herself *People* magazine. It's a simple pleasure she enjoys, and it works."

1

STAY ACTIVE

Exercising three times a week for about 30 minutes each session has been shown to cut cardiac morbidity and mortality by more than 10 percent, explains Seth Feltheimer, a general internist at New York–Presbyterian Hospital/Columbia University Medical Center.

To reap the maximum benefit from exercise, your pulse has to stay above 100 beats per minute. This requires more than an average walk, "where you might often stop and start at each corner and can't really get a chance to get the pulse up," Feltheimer adds. Franke agrees and recommends that you do whatever exercise you enjoy enough to do regularly and that is vigorous enough to increase your heart rate, be it walking with a neighbor or a high-intensity aerobics class at an exclusive fitness club.

"If you compare a person who is 30 pounds overweight but physically active with someone who is thin but a coach potato, you'll find the thin couch potato has a higher risk of premature death and of some chronic diseases, such as diabetes, heart disease and hypertension," Franke says. "Of course, the best combination is to be physically active and relatively close to normal weight, but if there was a choice, without hesitation I'd choose a little bit overweight but fit."

2

EAT HEALTHY

Reducing cholesterol intake by 20 percent and getting total cholesterol levels below 180 will improve a person's risk of heart disease by 20 to 30 percent, Feltheimer notes. Healthy diets should include at least five servings of fruits and vegetables a day, Franke declares. "This ensures that you get more vitamins and minerals, which most people don't do, and will likely increase fiber intake as well," he explains. "It will also be more filling, making you less likely to cheat and ingest more calories by nibbling on snacks."

"It's somewhat of a cliché, but the most important thing to do is to eat healthy and moderate your food intake," Franke notes. Feltheimer concurs and offers a strategy to help with moderation: "Don't eat until you can't eat anything else. You should always leave the table feeling you can eat a little more."

Moreover, as the experts note, many people's downfall is that they think of diets as temporary impositions that they can drop once they have reached a goal weight. Rather a truly healthy approach to eating means making lifestyle and behavioral changes that last. So find a diet you can truly live with for the long haul.

3

QUIT SMOKING

It's the advice you have probably been hearing for most, if not all, of your life. Yet despite the ubiquitous warnings, smoking is still the leading cause of preventable death in the U.S. The World Health Organization estimates that by 2015 tobacco will be responsible for 10 percent of all deaths—killing 50 percent more people than HIV will. Quitting smoking may be one of the most common New Year's resolutions, but it is also easily one of the most valuable to keep.

Cigarette smoke contains 69 known carcinogens and increases risks for most forms of cancer, particularly of the lung, kidney, larynx, head, neck, bladder, esophagus, pancreas and stomach. Smoking also increases blood pressure and the risk of heart disease while decreasing the "good," or HDL, cholesterol that lowers the risk of heart failure. The result is that every year, nearly 140,000 men and women in the U.S. die from cardiovascular disease attributed to smoking, according to the Centers for Disease Control and Prevention.

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Rewarding relationships with family, friends or even pets can relieve stress and may improve health.

The financial costs are also considerable. At $7 a pack, a pack-a-day smoker is spending almost $50 a week and $2,600 a year—and that does not include any of the financial costs associated with the medical problems of smoking.

4 DRINK APPROPRIATELY

Because of excessive drinking, which is defined as anything more than two drinks a day for men and one a day for women, over two million people in the U.S. have liver disease. Excessive drinking also increases the risk for heart disease, high blood pressure, stroke, inflammation of the pancreas and certain forms of cancer, especially cancers of the esophagus, mouth, throat, larynx and possibly the breast, colon and rectum.

Roughly 10 to 20 percent of heavy drinkers also develop alcoholic cirrhosis, or scarring of the liver; those with life-threatening cirrhosis may need liver transplants. In addition, Gibbons notes that statistics indicate "the more heavily you drink, the greater your risk for interpersonal problems."

Yet studies suggest that moderate drinking—for men, two or fewer drinks a day, and for women, no more than one—lowers the risk for cardiac disease and death by heart attack or stroke.

By these measures, moderate drinkers fare better than both heavy drinkers and abstainers. Researchers believe moderate drinking helps to ward off cardiovascular disease by thinning the blood and thus suppressing the formation of blood clots that can cause heart attacks and strokes. Alcohol also seems to enhance the body's ability to break down small clots.

5 RELIEVE STRESS

"We've known for years that chronic stress leads to increased risk of premature death, even in the absence of other things it's connected with, such as not taking care of yourself or high blood pressure," Franke explains. Some of the physiological mechanisms are clear. "Stress leads to your body producing cytokines or other inflammatory agents. In chronic stress, you carry on such responses to an abnormal extent, past what the fight-or-flight response was perhaps meant to handle, wearing down the body."

Furthermore, various studies have established that chronic stress can cause excessive blood clotting, leading to blockages and strokes, Feltheimer says. "It also decreases the responsiveness of the immune system. And with chronic stress, some cytokines can in essence degrade the structural stability of plaques lining blood vessels, which is analogous to making a blister more prone to popping. So that can contribute to a heart attack if it does pop."

"People need to focus on things that are within their control. It's wasted energy to stress about what's outside your control," Franke says. "Try to downshift and go with the flow, and if there are situations you can't downshift with, then avoid them if possible." ■

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